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Editorial

The Role of Caloric Intake and Output Imbalance in Atherogenesis

WITHIN THE PAST decade, facts and data have come to light which incriminate environmental factors, apart from innate ones, in ouman atherogenesis. Certain living habits or behavior patterns have significant motivating or at least modulating effects in the production of atherosclerosis. Actually, only two atherogenic factors have been established.

One of them is *overalimentation*. The epidemiology of coronary heart disease in practically every part of the world has shown a close parallelism between the food habits of a population and its degree of affliction with coronary disease. Ethnologic, racial, or climatic influences have been found to be negligible. The greater the amount of calories, and particularly those obtained from fats in a prevailing diet, the higher the incidence of coronary thrombosis. Experiments with animals have furnished additional evidence. Most animals are not known to suffer from atherosclerosis. Some species, however, can be made severely atherosclerotic through being fed special, rich diets. It is of interest that this atheromatous process is reversible. A disturbance in the lipoid metabolism always accompanies these processes in man and in the experimental animal. The exact pathogenesis of the disorder is unknown; it may take place mainly in the blood plasma or in the fibroplastic elements of the vessel walls.

In view of the foregoing, the role of diet in the pathogenesis of atherosclerosis is generally acknowledged. The second exogenous atherogenic element has been much slower in gaining recognition. This element is the habit of *sedentary living*. The reason for this slower recognition may stem from the fact that angina is brought on by effort and on occasion, a sudden or unusual overexertion triggers a coronary episode. In all such instances, however, atherosclerosis has been present for some time previously and has reduced the coronary reserve. The exertional trauma only reveals the underlying atherosclerotic condition. Physical inactivity as an atherogenic factor was clearly indicted by the Medical Research Council of Great Britain.[1] When J. M. Morris and his group investigated the coronary morbidity and mortality in the different social strata of the London population, they found that the number of heart attacks in the uppermost social class was three times higher than in the lowest. When groups with similar salaries, diet and living habits were explored, it was found that the chances of suffering coronary thrombosis were at least one-third higher in people with physically inactive occupations (clerks, switchboard

operators, truck drivers) than in the sum total of the population. The incidence of heart attacks more than tripled when the sedentary group was matched against heavy laborers, miners, transport workers or farmers. These surveys cover hundreds of thousands of people and carry conviction. It would seem that sedentary living conditions predispose people to coronary heart disease. One may even venture to say that sedentary working conditions present an occupational hazard. Increasing automation of labor naturally equalizes the chances of coronary heart disease; more recent statistics in this country have indicated such a trend. It has become apparent from all available sources of coronary epidemiology that coronary heart disease can be correlated with industrialization. Concurrent with the multiplication of labor-saving devices and the dwindling duties of human musculature, coronary heart disease has increased.

Overemotionalism has been blamed frequently as a contributing factor to the cause of coronary heart disease. This has not been proven. No characteristic emotional qualities have been detected in the stricken. Naturally, emotional trauma, just as exertional trauma, is more injurious to an individual already suffering from atherosclerosis. It is a fact, too, that overemotional people have a tendency to overeat. People with emotional overdrive frequently suffer from mental fatigue and insomnia and, as a panacea, indulge in more and more physical rest. This is a boomerang because sedentary habits not only nourish emotionalism but also encourage the vascular derangement.[2]

Consequently, only habitual overalimentation and sedentary living habits have been established, with sufficient degree of conclusiveness, as exogenous atherogenic elements thus far. This question arises: Are these two elements separate, independent factors? The answer may well be no. These elements may be interdependent in a simultaneous assault on biochemical integrity. Circumstantial evidence of such an assumption is at hand.

For instance, the production of atheromatosis in animals through high cholesterol feeding has been achieved, usually, with the support of antithyroid medication; by suppressing thyroid activity the animals have been made sluggish. Thiouracil even prevents the antiatherogenic action of estrogen in the experimental animal.[4] Hypothyroidism in man is generally concurrent with hypercholesteremia. Although high caloric diets have produced high cholesterol blood levels in men with average physical activity, they have failed to do so when the subjects were kept on a program of strenuous physical activity.[5] The rather odd observation that laborers from southern Italy, habitually obese, suffer less from coronary disease than others who "grow" fat[6] also bears out the theory that overalimentation in itself may not be atherogenic without the added factor of physical inactivity.

The assumption that *surplus caloric intake in conjunction with deficient energy expenditure* combine to produce atherosclerosis suggests itself by the daily experience of the clinician. The younger victims of coronary thrombosis are usually men who have been active, even physically powerful individuals, who for various reasons have slipped into a kind of muscular retirement. They are the men who, due to a sore back or some other accident or ailment, became pinned to a desk job. They are the middle aged bachelors who have wed good cooks and housekeepers. In many instances the acquisition of an automobile starts the muscular "hibernation." The list could be enlarged ad infinitum.

A dramatic illustration of the importance of physical activity is the case of a lawyer, now 65 years old. He had always been a versatile athlete. In 1944, at the age of 51, he had suffered a coronary thrombosis and cerebral embolism. Two years later he had another episode of coronary thrombosis and myocardial infarction. A third attack occurred in 1948, complicated by a pulmonary embolism. From his first attack in 1944 his physicians insisted on greatly restricted activity and an abundance of rest. In short, the patient was invalided. However, shortly after recovery from his third attack, the patient himself decided that exercise would help him since obviously rest did not. He eluded the watchful eye of his concerned family and resumed tennis. Ever since he has gradually increased athletic activities. Various sport activities carry him through 12 months of the year. During the summer he

plays vigorous tennis, sails, swims, gardens and rides horseback. During the winter he ice skates, difficult figure skating at that, for hours at a time. He never suffered another coronary attack or angina pectoris. Recent check-ups have revealed his condition to be excellent except for abnormal electrocardiograms reflecting old scars. In giving his history, he volunteered that his first heart attack was preceded by many months of physical inactivity due to professional duties as an arbitration lawyer. The second and third attacks, he thought, were brought about by too much "ordered" rest. Unusual as this case may be, it highlights the contention which has been stressed recently that exercise does far more for the stimulation of collateral circulation than anything medicine or surgery can offer.[6,7] This case also provokes thought regarding the all too liberal advice of restriction of physical activity after recovery from a coronary thrombosis and myocardial infarction. Actually, such advice may raise the irksome question of iatrogenesis.

Why should relative physical inactivity lead to coronary heart disease? The large voluntary muscle mass of the body not only serves locomotion but has essential metabolic and circulatory functions. One may take a cue from the consequences of prolonged rest, particularly bed rest, which interferes with the dynamics of the circulation and paves the way for phlebothrombosis or pulmonary edema. One may speculate on the many humoral disturbances subsequent to rest as exemplified by anemia and calculosis. One may argue that lack of conditioning overtaxes the oxygen demand and supply balance in the coronary system, thus creating an increased vulnerability of the coronary arteries to the atherosclerotic affliction. On the other hand, considering the plasma lipid balance, one may speculate that the powerful arteriolar sluice mechanism set in motion by exercise removes burdensome lipids from the plasma (by consumption of acetylcholine?). It may be assumed that increased steroid production during exercise burns lipid material. There is a possibility, too, that capillary cell activity within muscles, multiplied several hundred times by physical stress consumes lipids. The inability to raise cholesterol levels in overactive individuals lends substance to such thinking.[4]

Man's natural history offers a plausible reason why too many conveniences plus an overabundance of food upset the humoral mechanisms. Primitive man contended with great physical hardships and little food. Progressively, man has become amazingly resourceful in his adaptation to lean larders and hard labor. However, when man's genius reversed his early predicament he burdened himself with too little toil and too much food. Catapulted into this new condition within a scant few centuries, his body finds itself phylogenetically inadequately equipped to cope with the stress of this new mode of living.

In conclusion, a critical survey of current literature, common clinical experience, as well as theoretic considerations suggest that a disproportion between caloric intake and output is an important, possibly even the true exogenous atherogenic factor. Simply, it would appear that habitual overalimentation without corresponding energy disbursement initiates a chain of metabolic disorders in a predisposed individual that results in coronary heart disease. Although it is not held that this concept contains all the answers to a most complex problem, it is a plausible and workable theory with important practical implications.

In spite of the fact that the evidence is far from complete, and much more experience and investigation are needed to support the theory of caloric imbalance, it seems appropriate and wise to incorporate the theory in therapeutic planning just as is the case with diet, the need and value of which are still questioned by some skeptics. Naturally, it means to stress the need for regular and methodical physical training and conditioning wherever and as much as is feasible. Sooner or later an optimal balance scheme of diet and exercise might be forthcoming. The risk is nil. The benefits may be incalculable.

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Symposium on Mitral Regurgitation

Mitral Insufficiency*

Historical and Clinical Aspects

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OUR PRESENT concept of mitral insufficiency has evolved during the past fifty years.[10,20,21] Its existence, as a clinical entity, was nearly denied early in the century and with this view the apical systolic murmur was relegated to an unimportant position. Following this, there was a gradual appreciation that both organic and functional mitral insufficiency were of clinical significance. This was based on long term observation of patients with acute rheumatic fever and rheumatic heart disease and a renewed interest in chronic valvular disease of all types. Studies of the systolic murmur and the development of phonocardiography helped to clarify the problem. Current concepts of mitral valvular disease (both stenosis and insufficiency) are based on new knowledge of the anatomy and physiology of this valve acquired through surgical procedures, a review of the pathology of the valve, and right and left heart catheterization. While as yet incomplete, they are quite different from those of the era preceding mitral valve surgery only a decade ago.

HISTORICAL REVIEW

Probably the first appreciation of the effect of mitral valvular disease on the pathologic physiology of the cardiorespiratory mechanism was by Vieussens,[19] (1715) who recognized that dyspnea in mitral stenosis was the result of pulmonary congestion secondary to the narrowed mitral orifice. Corvisart[6] (1812) and Laennec[14] (1827) described signs which they attributed to disease of the mitral valve—"a purring or whirring vibration, or thrill" and "a particular sensation perceived by the hand in the cardiac region . . . as a sign of ossification of the valves and particularly of the mitral." Laennec, the discoverer of the stethescope, described murmurs heard over the heart as a "bellows sound" and resembling the sound of a rasp or file. He recognized that the louder murmurs were often associated with contraction of the mitral or aortic valve orifices and that the signs from the two valves were located in different areas. Neither Corvisart nor Laennec appreciated the mechanism of production of these signs or their timing in the cardiac cycle. However, Laennec recognized that the softer murmur (bellows sound) was frequently heard when the valves were found to be normal—". . . and as it is, moreover, very common when the heart is perfectly sound, we must lay no stress on it as a sign unless it be combined with other circumstances calculated to confirm the diagnosis" —it would seem an appreciation of the so-called functional systolic murmur.

Hope[13] (1832) recognized both mitral stenosis and insufficiency as distinct lesions. He appreciated the systolic time of the murmur associated with mitral insufficiency and that severe mitral regurgitation was attended with marked changes in both the left auricle and ventricle with changes even transmitted back to the right heart. "When the mitral orifice is permanently patescent, so that, at each ventricular contraction, blood regurgitates into the

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auricle, this cavity suffers in a remarkable degree: for it is not only gorged with blood which it cannot transmit, but, in addition, sustains the pressure of the ventricular contraction. Permanent patescence of the mitral orifice, therefore, constitutes an obstruction to the left side of the heart, and the effect of this, as of contraction of the orifice, may be propagated backwards to the right side." He noted slight regurgitation might occur without stenosis of the valve—"... a contraction of the chordae tendineae preventing the margins of the valve from coming in perfect opposition: and in this way is to be explained a phenomenon which I have frequently noticed; namely, that a murmur from regurgitation frequently accompanies the first sound, when none attends the second." And again he recognized that high degrees of stenosis were accompanied by a less loud (systolic) murmur—"with respect to the mitral, the murmur is diminished when the contraction of the orifice is extreme: when, for instance the aperture does not exceed two or three lines in diameter; for then, the quantity of blood is not sufficient to create a loud murmur." While Hope, like Laennec, did not fully appreciate the timing of the diastolic murmur of mitral stenosis his observations and views on mitral stenosis and insufficiency were remarkably accurate and sound extremely contemporary.

Williams[22] (1835) was the first to recognize the diastolic timing of a murmur associated with obstructive disease of the mitral valve and the fact that such a murmur "followed the second sound" (which he correctly associated with the semilunar valves). He noted its occurrence in the earlier part of diastole and independent of the auricular contraction—an essentially diastolic and not merely a presystolic murmur—a description unheeded for nearly a century. Austin Flint[8] (1859) had an excellent understanding of valvular disease and considered the mitral regurgitant (systolic) murmur the one most frequently met with in organic disease of the heart. He believed that the murmur might be produced without regurgitation but recognized that a murmur in this area, transmitted widely, was strong evidence for it. His clinical appraisal of this lesion was fairly accurate in the light of our present-day views. "Clinical observation shows that mitral regurgitation is long borne without serious inconvenience, especially if mitral contraction does not coexist. Symptoms therefore do not afford much aid in an early diagnosis of mitral insufficiency." For the remainder of the 19th century apical systolic murmurs were largely regarded as the result of organic mitral insufficiency and mitral incompetence was the most common valvular lesion diagnosed. The prognosis of this finding was often unduly pessimistic and patients were put in bed unnecessarily.

Early in this century a change of view occurred as the result of the teachings of Graham Steell[18] (1906) and Sir James Mackenzie[16] (1916). Steell recognized that mitral incompetence often accompanied mitral stenosis but believed its presence was not significant. He stressed the importance of muscle failure rather than disease of the valve in mitral regurgitation. Mackenzie agreed with this view and to combat unwarranted invalidism taught that the apical systolic murmur could be disregarded when unaccompanied by other signs of heart disease. Sir Thomas Lewis[15] continued this teaching and stressed the importance of an apical systolic murmur was to hunt carefully for a diastolic one, in that a systolic murmur alone was not evidence of a diseased valve. Cabot[4] (1926) recognized that mitral insufficiency might exist without stenosis but held it to be of no importance and felt that a diagnosis of mitral regurgitation without mitral stenosis was not justified. The pendulum had swung too far and a generation ago Sprague and White,[17] Levine and others[1,9] again recognized the diagnostic and clinical importance of the apical systolic murmur and there was a gradual awakening to the importance of mitral regurgitation in various cardiac conditions.[12] However, it remained for the introduction of mitral valve surgery to stimulate interest in all phases of mitral valvular disease. For the first time incompetence of the mitral valve is being seen in its true perspective.

Mechanism of Production

The exact mode of closure of the normal mitral valve is still debated. The cusps, chordae tendinae and papillary muscles are all important in this function, as is the ring itself,

which is reduced in circumference during systole. Brock,[3] whose opinions on mitral regurgitation are based on observation of valve function at operation as well as careful studies of the pathologic changes of diseased valves, with and without operation, has stressed many important facts relative to both mitral stenosis and insufficiency. "The valve mechanism extends over a distance of some 5 cm, and a lesion may affect all parts of it or one part more severely than another. A lesion at any level can seriously interfere with the mechanism and it is not always the actual valve cusps that are most affected." He points out that the old view that mitral regurgitation results from a mild rheumatic valvulitis and mitral stenosis from a more severe attack is an "erroneous oversimplification" and that true mitral insufficiency is usually caused by the most severe grades of damage to the valve. He lists six mechanisms which may be operative in the production of mitral regurgitation with two or more usually coexisting in the severe cases.

From observation at operation Brock describes three degrees of mitral incompetence: (1) A small regurgitant stream from a grossly stenosed orifice; (2) a moderately powerful regurgitant stream from a narrowed but not markedly stenosed valve; and (3) a powerful regurgitant stream with a large orifice (equal to an area of the aortic outlet, at times). In the first type with a severe grade of stenosis the regurgitation is usually of minor importance and is often improved by operation to enlarge the valve. The second type usually represents the most severe grades of damage to the valve mechanism with all parts of the valve involved. A densely fibrotic process may prevent dilatation of the ring and extreme incompetence of the valve. Present surgical procedures offer no help in this type of mitral disease. Those with severe mitral regurgitation with a large orifice during systole may have a mitral ring larger than normal. The left auricle and ventricle are usually much enlarged in this type and myocardial failure may increase the dilatation of the ring, producing further insufficiency.

Diagnostic Evaluation of Patients

The evaluation of patients with acquired valvular disease for cardiac surgery has contributed a good deal of clinical and laboratory information which is pertinent to mitral insufficiency as well as stenosis. Wood[23,24] has reported a detailed study of 300 patients with mitral valve disease one-half of whom were considered unsuitable for operation. "Pure" mitral stenosis was present in 35 per cent of the series with 6.6 per cent more having trivial mitral incompetence. Serious incompetence was evident in 12.3 per cent, while 15.6 per cent had "pure" mitral regurgitation. There was no patient with significant mitral insufficiency in whom a systolic murmur was not heard. "It can no longer be seriously maintained that a mitral systolic murmur is of little value in determining the presence or absence of mitral incompetence." A 3rd heart sound was not heard in any of the patients with pure mitral stenosis but was present in 85 per cent of those with well developed incompetence and 25 per cent with mild mitral incompetence. An opening snap and a loud first sound were considered excellent talismans against the presence of serious mitral insufficiency. Atrial fibrillation was more frequent in cases with pure stenosis than with pure insufficiency but was most often seen in patients with mixed stenosis and insufficiency. It could not be correlated with the size of the mitral orifice but rather was related to age and distention of the left auricle. Heavy calcification of the valve is uncommon in pure incompetence but occurred in one-half of the cases with combined stenosis and insufficiency. In approximately 70 per cent of the patients in whom mitral regurgitation was the major hemodynamic fault it was considered a serious lesion and one in which surgical treatment would have been considered, if a satisfactory operation had been available.

Brigden and Leatham[2] followed a group of 30 patients with mitral incompetence for a three-year period. Five-sixths of the patients were men and over one-half were between the ages of 50 and 60 years. A history of rheumatic fever was rare. One-third of the group had subacute bacterial endocarditis and one-half of these succumbed. In all of the bacterial endocarditis cases a loud apical systolic murmur was present before the infection occurred. The patients

were symptomless except for palpitation, usually related to premature contractions. Atrial fibrillation occurred in 8 of 30 patients. Heart failure occurred in nine patients while under observation and six of these died within a year. A loud pansystolic murmur of at least grade 4 intensity was present in every patient and a 3rd heart sound was heard in one-half of the cases and was considered due to increased filling of the left ventricle. Postmortem examinations done on nine patients disclosed mitral insufficiency without stenosis in all instances. Ellis, Abelmann and Harken[7] have recently summarized much of our present knowledge pertinent to the selection of patients for mitral valve surgery, based on experience with 1,000 patients who had undergone cardiac surgery.

HEART SOUNDS AND MURMURS

Auscultation, carefully performed and augmented when indicated by phonocardiography, is the most valuable single diagnostic procedure in mitral valvular disease. The characteristic murmur of mitral incompetence is a loud apical pansystolic murmur embracing both the first and second sounds. A palpable thrill is common. The first heart sound is soft or normal and sound tracings demonstrate its presence as well as the duration of the murmur into or past the second sound. A loud third heart sound is often present and a short early low frequency diastolic murmur is common. The duration of the diastolic murmur is of much significance. A short atrioventricular diastolic murmur is characteristic of unusually rapid ventricular filling and occurs in a variety of conditions many of which are not associated with a diseased A-V valve (thyrotoxicosis, anemia, patent ductus, ventricular septal defect and atrial septal defect). Thus, a short mitral diastolic murmur is confirmatory evidence for marked mitral insufficiency. A prolonged diastolic murmur, presystolic murmur, accentuated first heart sound or opening snap are evidence against serious mitral incompetence and for an appreciable grade of stenosis. The murmur of mitral regurgitation must be differentiated from functional murmurs, the murmur of aortic stenosis and Roger's murmur. This is usually not difficult if the location, quality, duration and radiation of the murmur is correlated with other clinical and laboratory data.

CATHETERIZATION FINDINGS

The pressure gradient between the left ventricle and atrium during systole is much greater than between the ventricle and the aorta and results in a large reflux into the left atrium during ventricular systole, if the mitral valve is incompetent. A sharp reduction in cardiac output is the major physiologic defect in mitral insufficiency and it has been estimated that regurgitation through an extent of one-fifth the cross-sectional area of the valve orifice may reduce the cardiac output 50 per cent. The left atrium compensates for the mitral insufficiency by a greater output of blood, attributable to several factors. The left ventricle develops dilatation and hypertrophy to accomplish the increased work required of it. At times this may be extreme. Left atrial pressure may be very high during ventricular systole but it falls to the ventricular level in diastole with the mean left atrial and pulmonary artery pressures lower than in mitral stenosis of comparable severity. Recent observations[5,11] with new laboratory technics have contributed data on the quantitative aspects of mitral regurgitation including estimates of the cross-sectional area of the valve orifice and the volume of regurgitant flow.

Clinical Course

The clinical course of the patient with mitral insufficiency may be quite varied. Mild degrees may be associated with no cardiac enlargement and at times be well borne for a normal life span. However, mild asymptomatic lesions of this type are especially susceptible to superimposed bacterial infections. This represents not only a threat to the life of the patient but the minimal incompetence is often changed to a serious one. Severe grades of mitral regurgitation are less common than comparable degrees of mitral stenosis and when due primarily to organic valve disease (rheumatic) are evident sooner after the infection than stenotic lesions, and tolerated less well. Patients with a combined lesion of mitral stenosis and insufficiency, where the latter is of moderate degree, usually

do less well than more severe grades of stenosis with little or no regurgitation. Left auricular and ventricular enlargement are the rule and atrial fibrillation is most frequently seen with such a combination. This lesion is not amenable to any current surgical procedure.

Enlargement of the left atrium is frequent in mitral insufficiency as well as in stenosis. A systolic expansile pulsation of the atrium, seen on both borders of the heart on fluoroscopic examination (P-A view), is regarded as pathognomonic of organic regurgitation by some. Aneurysmal dilatation of the left atrium is more often seen with mitral incompetence than stenosis and auricular fibrillation and disease of the auricular muscle are apt to be concomitant findings in this condition. Relative (functional) mitral insufficiency is seldom a trivial condition. This dysfunction of the valve, secondary to myocardial disease or left ventricular enlargement from other causes, usually represents serious underlying disease, which may be of greater prognostic importance than the valvular lesion per se.

Treatment

Present-day therapeutic measures offer little specific help to the patient with severe (organic or functional) mitral insufficiency. Congestive heart failure occurs later in the course of the disease with severe incompetence than with stenosis, but when it occurs the downhill course is usually more rapid. Fortunately, great strides have been made in the prevention of rheumatic heart disease and bacterial endocarditis during the past few years An apical systolic murmur without cardiac enlargement must no longer be regarded as "innocent" or one in which nothing can or need be done. The first step is to determine whether or not the murmur represents mitral valve insufficiency or if it is a "functional" (noncardiac origin) murmur. If all apical systolic murmurs are viewed with suspicion and an attempt made to explain their origin, few errors will be made. It can be expected that rheumatic heart disease will become less frequent and less severe with the adequate treatment of streptococcic upper respiratory infections by the proper antibiotics. Subsequent daily prophylaxis of all patients with acute rheumatic fever and rheumatic heart disease, both young and old, may prevent the progression of organic valvular lesions in established cases. The early recognition of bacterial endocarditis with adequate and specific antibiotic therapy will prevent the conversion of minimal benign mitral insufficiency into a severe grade of incompetence in many instances as well as reduce the immediate mortality of this disease.

The protection of a mild but most susceptible healed mitral valvulitis to superimposed infection during surgical procedures must be constantly emphasized. Operations on the nose and throat, genitourinary tract and tooth extractions are the greatest offenders. Pre- and postoperative prophylaxis will nearly eliminate this complication. Penicillin and penicillin plus streptomycin remain the important antibiotics for use in this field. With the decrease in aortic valve disease (rheumatic and luetic) and the improved management of hypertensive heart disease the incidence of severe functional mitral insufficiency should decrease significantly within the next few years.

It is thus evident that the real province of medical therapy in mitral insufficiency lies in the field of preventive medicine. At present, there is a large pool of patients with this ailment awaiting the development of effective operations to aid their immediate future. It seems likely, however, that a generation from now the need for such corrective therapeutic measures will be minimal.

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Clinical and Hemodynamic Observations In Pure Mitral Insufficiency*

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MITRAL insufficiency unaccompanied by other valvular lesions is relatively uncommon. In Cabot's series of 1,846 autopsies on patients with heart disease there were only seven instances of pure mitral insufficiency, in contrast to 107 of mitral stenosis.[1] Other postmortem and clinical studies of patients with mitral valve disease confirm a similar incidence of pure mitral insufficiency in relation to mitral stenosis.[2–4] Several reports describing the clinical findings in patients with pure mitral insufficiency have appeared[2,5,7,10] and recently hemodynamic observations, primarily concerned with data obtained at right heart catheterization, have been published.[3,8,13] Severe pulmonary hypertension and markedly increased pulmonary arteriolar resistance were seldom noted[13] although, on occasion, moderate elevations were encountered.[3,8,12] The characteristics of the left atrial pulse contour in mitral insufficiency have been described,[14–20] but such studies have generally not been combined with left ventricular catheterization.

The present communication is an analysis of findings in a group of patients considered to have pure mitral insufficiency. Hemodynamic findings in the left heart and the lesser circulation are emphasized and selected pathologic material is included.

CLINICAL MATERIAL AND METHODS OF STUDY

Twenty-three patients were studied. The typical clinical findings of mitral insufficiency were present in all. Three patients had associated essential hypertension and they are specifically noted in the tables. The diagnosis of mitral insufficiency as the sole valvular lesion was established at postmortem examination in three patients, at operation in five, by the absence of a diastolic gradient between left atrium and left ventricle and the presence of a characteristic left atrial pressure pulse in nine, and by the clinical picture and the characteristic left atrial pulse contour in the remaining six.

Right heart catheterizations were carried out in 20 patients; all 23 patients had left heart catheterization by the transbronchial route. The details of the latter technic have been reported elsewhere.[21]

RESULTS AND DISCUSSION

CLINICAL FEATURES

The clinical findings in the entire group are summarized in Table I. There were 13 female and ten male patients. Previous reports have stated that mitral insufficiency occurs predominantly in males.[1,3,6] In 13 patients a definite history of rheumatic fever was elicited. Four patients had a history of bacterial endocarditis. Hemoptysis was encountered in seven patients. Ten patients had had heart murmurs for at least 15 years, a finding in support of the concept that mitral insufficiency may run a protracted course.[22,23] All patients experienced dyspnea of some degree; however, 13 of them stated that fatigue was a symptom of equal or greater magnitude. The prominence of fatigue in the symptomatology of mitral insufficiency has been emphasized previously.[9] Angina pectoris was a significant symptom in six patients, none of whom had systemic hypertension. A loud apical systolic murmur was present in every

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TABLE I

Clinical Findings in 23 Patients with Pure Mitral Insufficiency

Patient	Age	Sex	History of rheumatic fever	Years known murmur	Fatigue	Dyspnea	PND	Grade systolic murmur	Syatolic thrill	Grade diastolic murmur	3 kg diuresis	Diagnosis made by
Group I												
ES	40	F	+	30	3	2	0	4	0	0	0	Left heart catheterization
MG	21	F	+	7	0	1	+	3	+	1	0	Clinical and L.A. pressure
GB	31	F	+	23	3	1	0	3	0	0	0	Surgery
LG	47	F	0	19	3	2	+	3	0	2	0	Left heart catheterization
AE	60	F	0	48	0	2	+	4	0	0	0	Clinical and L.A. pressure
AP	40	F	+	17	2	2	0	4	+	0	0	Left heart catheterization
WB	20	M	+	9	2	1	0	3	0	0	0	Left heart catheterization
KS	28	M	+	9	0	2	+	4	+	0	0	Left heart catheterization
FM	30	F	+	8	1	1	0	4	+	1	0	Surgery
LMc*	59	M	0	10	1	3	—	3	0	0	+	Left heart catheterization
LB	27	M	+	21	2	2	+	4	+	0	0	Surgery
LJ	38	F	+	19	0	2	0	3	0	0	0	Clinical and L.A. pressure
BS	49	M	+	6	2	3	+	3	0	0	+	Left heart catheterization
Group II												
FT	56	M	0	16	2	3	+	4	+	0	+	Left heart catheterization
DS	18	F	0	2	1	3	+	4	+	0	+	Clinical and L.A. pressure
AW*	49	M	+	32	4	3	+	4	+	1	+	Autopsy
RZ	23	F	+	9	3	2	+	4	+	2	+	Autopsy
AA	37	F	0	12	3	3	+	4	0	0	0	Left heart catheterization
LF	29	F	+	7	2	3	0	4	+	2	0	Clinical and L.A. pressure
HT*	47	M	0	2	2	2	+	4	+	0	+	Left heart catheterization
WC	49	M	0	0	1	2	+	3	0	0	+	Clinical and L.A. pressure
RH	54	M	0	5	3	3	+	4	+	0	+	Autopsy
BM	19	F	0	14	3	2	0	4	+	0	+	Surgery

M = male, F = female, "+" and "0" indicate presence or absence of a history of rheumatic fever. Fatigue, dyspnea, systolic and diastolic murmurs were graded on a 0 to 4+ scale. PND = paroxysmal nocturnal dyspnea.

* Patients with systemic hypertension in this and other tables.

patient, and was usually accompanied by a thrill. Soft apical diastolic murmurs were also present in six patients. These did not have the auscultatory features of the murmur of mitral stenosis and are not infrequently heard in patients with pure mitral insufficiency.[2,3,6,8]

The patients have been divided into two groups on the basis of right ventricular systolic pressures. Group I consists of 13 patients, ten of whom had normal or only slightly elevated pressures. The three patients who did not have right heart catheterization are also included in this group. Group II is composed of ten patients in whom the systolic pressure in the pulmonary artery or right ventricle exceeded 55 mm Hg. It is of interest that there was no striking difference in the ages of patients in the two groups; furthermore, in group II, the pulmonary hypertensive group, there were several patients in whom murmurs had been discovered a relatively short time before study. In general, patients in group II had more severe symptoms, and all but two had considerable fluid accumulation as evidenced by a weight loss of at least 3 kg when diuretics were administered.

ELECTROCARDIOGRAPHIC AND RADIOGRAPHIC STUDIES

Electrocardiogram: Electrocardiographic evidence of left ventricular hypertrophy has been reported to be useful in detecting the presence of insufficiency in patients with combined mitral valve lesions.[3,24] Pertinent electrocardiographic findings in the present group of 23 patients with pure mitral insufficiency are present in Table II. The criteria employed in the diagnosis of ventricular hypertrophy were those previously suggested[25] and are based on an extensive compilation of normal ranges of voltage and activation time.[26] The electrocardiographic diagnosis of atrial enlarge-

TABLE II

Electrocardiographic and Roentgenographic Observations

Patient	Rhythm	ECG			X-ray			
					Enlargement			Pulmonary vascular markings
		Atrial enlargement	Axis deviation	Ventricular hypertrophy	Left atrium	Left ventricle	Right ventricle	
Group I								
ES	Sinus	0	Left	0	1+	2+	0	N
MG	Sinus	Left	N	0	1+	0	0	N
GB	AF		N	Left	3+	2+	2+	N
LG	AF		N	0	2+	2+	1+	N
AE	Sinus	AV block	N	0	1+	2+	0	N
AP	Sinus	AV block	N	Left	3+	2+	1+	N
WB	Sinus	0	N	Left	1+	1+	1+	N
KS	Sinus	Left	N	Left	1+	1+	0	N
FM	AF		N	0	2+	2+	1+	I
LMc*	Sinus	Left	N	Left	N	4+	2+	N
LB	Sinus	Left	N	Left	2+	1+	0	N
LJ	AF		N	0	+			
BS	AF		Left	0	3+	3+	2+	I
Group II								
FT	AF		N	Left	3+	2+	1+	I
DS	AF		N	Left	4+	2+	2+	I
AW*	AF		N	Left	3+	3+	2+	I
RZ	AF		N	Combined	4+	1+	3+	N
AA	Sinus	Left	N	0	2+	3+	2+	N
LF	AF	N	N	0	4+	2+	2+	N
HT*	Sinus	0	N	Combined	3+	2+	2+	N
WC	Sinus	Left	N	Left	2+	3+	2+	I
RH	Sinus	AV block	Left	Left	2+	3+	2+	N
BM	AF		N	Right	3+	2+	2+	I

A.F. = atrial fibrillation. Roentgenographic evaluation of chamber size graded on a 0 to 4+ basis. Pulmonary vascular markings designated as normal (N) or increased (I). Patient L. J. had incomplete roentgenographic study.

ment was made by the method of Macruz *et al.*[27] utilizing the ratio of the duration of the P wave to that of the P-R segment.

Six of the 13 patients in group II had left ventricular hypertrophy, two had combined hypertrophy, and one had right ventricular hypertrophy. Isolated right ventricular hypertrophy has previously been reported in patients with predominant mitral insufficiency.[28] The electrocardiograms of the 12 patients with sinus rhythm were analyzed for evidence of atrial enlargement. Three patients had prolongation of the P-R interval and were therefore excluded. Six of the nine suitable tracings fulfilled the criteria for left atrial enlargement.

X-Ray Findings: A summary of the roentgenographic examinations is also presented in Table II. The left atrium was enlarged to some extent in all but one of the 23 patients. Of the ten patients with markedly enlarged left atria, three were in group I and seven were in group II. Nine of the ten patients in group II demonstrated considerable enlargement of the left ventricle, while only seven of 13 patients in group I showed a comparable increase in the size of the left ventricular shadow. Significant right ventricular enlargement was noted in only three patients in group I, but was present in nine of the patients with pulmonary hypertension in group II. In addition, six of the

TABLE III
Right Heart Catheterization Data

Patient	Pulmonary artery pressure	Pulmonary artery mean pressure	Right ventricle S/D	PC wedge tracing		Cardiac index (l/min/m^2)	Pulmonary arteriolar resistance (dynes sec cm^{-5})
				V wave	PC mean		
Group I							
ES	15/2	10	28/10	Non-phasic	5	2.47	160
MG	28/13	16	24/4	23	10.5	3.36	86
GB	28/11	17	31/6	26	15.5	2.44	32
LG	25/11	18	24/3	Non-phasic	11	1.87	209
AE	28/13	19	25/6	15	9	3.26	171
AP	28/13	19	26/3	Non-phasic	15	2.53	79
WB	30/18	20	32/7	Non-phasic	9	3.35	142
KS	32/20	21	36/6	Not entered		3.56	
FM	36/21	24	36/7	Not entered		4.96	
LMc*	37/21		35/5	Not entered		Not performed	
LB	No cath.						
LJ	No cath.						
BS	No cath.						
Group II							
FT	56/20	35	56/8	43.5	21	2.04	313
DS	Not entered		57/8	Not entered		Not performed	
AW*	59/24	39	57/8	47	26	3.58	250
RZ	61/25	40	59/9	Non-phasic	17	2.05	729
AA	64/42	53	60/18	52	31	1.35	798
LF	68/32	48	64/8	Non-phasic	29	2.49	384
HT*	Not entered		70/24	Not entered		Not performed	
WC	79/37	52	77/14	Not entered		1.38	
RH	84/36	54	76/6	34	23	Not performed	
BM	105/50	67	100/15	Non-phasic	25	2.36	1017

All pressures in mm Hg.

latter group also showed prominence of the pulmonary conus, and four had increased pulmonary vascular markings. Calcification in the region of the mitral valve was noted fluoroscopically in only two patients. It is of interest that nine of the ten patients with very large left atria had atrial fibrillation. Of the patients in sinus rhythm, the electrocardiographic and roentgenographic methods of determining left atrial enlargement did not always correlate.

Angiocardiogram: Angiocardiography with peripheral venous injection was performed in 11 patients. Although some authors have reported angiocardiography to be helpful in differentiating mitral stenosis from mitral in-

sufficiency[29,30] this has not been confirmed by the experience at the National Heart Institute.[31] In general, the procedure was helpful only in substantiating estimates of chamber size obtained at fluoroscopic and roentgenographic examinations.

RIGHT HEART CATHETERIZATION

Pertinent data from the right heart catheterizations are presented in Table III. As noted above, the incidence of marked pulmonary hypertension in the series was relatively high. Pulmonary arteriolar resistance could be calculated in 12 patients. As might be anticipated, no patient in group I had an increased resistance (above 250 dynes sec cm^{-5}), while in group II, five showed significant elevations. Three of these values were extremely high, ranging from 729 to 1017 dynes sec cm^{-5}. In a sixth patient in group II (R. H.) cardiac output was not measured, but a markedly elevated mean gradient (31 mm Hg) across the pulmonary vascular bed was demonstrated. These findings are in contrast to those of Wood who noted mild elevations of pulmonary arteriolar resistance in only 10 per cent of patients with pure mitral insufficiency.[3] In Pedersen's five patients, one showed an increased resistance.[8]

Determinations of forward cardiac output by the direct Fick method were carried out in 16 patients. Ten patients had abnormally low cardiac indices, i.e., below 2.6 $l/min/m^2$. Eight of these ten patients described fatigability as a prominent symptom.

Pulmonary Wedge Tracings: In only seven patients could a pulmonary capillary wedge tracing suitable for analysis of contour be obtained. Nine other wedge tracings were nonphasic, while in four additional patients the catheter could not be wedged. Wedge and left atrial pressures were compared in the seven patients with satisfactory wedge tracings. In only three instances was a good correlation of both excursion and contour noted; the remaining four wedge tracings resembled the left atrial pulse contour but exhibited smaller excursions. It should be pointed out, however, that these tracings were not taken simultaneously. Several authors have emphasized the value of pulmonary capillary wedge tracing analysis in the differentiation of mitral stenosis and insufficiency.[8,9,11,32] The present wedge tracings were analyzed in a manner similar to that employed with the left atrial pressure tracings. The ratios previously found to be of diagnostic value in left atrial pulse contour analysis[19] did not yield values indicative of mitral insufficiency when applied to the wedge tracings; however, wedge tracings of patients with mitral stenosis were not analyzed in similar fashion for comparison. The rate of the Y descent divided by the height of the V wave, a ratio found by Wood to be useful for differentiating mitral stenosis from insufficiency in the wedge tracing,[32] was found to be within the range characteristic of mitral insufficiency in only two of the seven tracings. These data, therefore, support the finding that the pulmonary capillary wedge tracing in mitral insufficiency is only occasionally diagnostic.[2,29,33,34]

LEFT HEART PRESSURES

Left Atrial Pulse Contour: The data obtained at left heart catheterization are summarized in Table IV. In this clinic three methods of left atrial pressure pulse contour analysis have been found useful in differentiating mitral stenosis from pure mitral insufficiency:[19] (1) The ratio of the rate of the Y descent (i.e., the fall of the V wave) to mean left atrial pressure (Ry/MLAP); (2) the ratio of the Y descent in the first 0.1 sec to the mean left atrial pressure; and (3) in patients with sinus rhythm, the ratio of the pressure at the peak of the V wave to that at the peak of the A wave. In those patients with pure mitral insufficiency previously reported, the Ry/MLAP ratio always exceeded 4.0, the Y descent in 0.1 sec/MLAP exceeded 0.5, and the V/A ratio exceeded 1.4. None of the patients with mitral stenosis had ratios in the mitral insufficiency range. Twenty of the 23 patients in the present series satisfied these criteria considered diagnostic of mitral insufficiency. One of the remaining three patients (L. G.), had an Ry/MLAP ratio below 4.0, although the fall in 0.1 sec exceeded 0.5. The other two patients (W. B. and E. S.), had only mild symptoms and low mean left atrial pressures. Ry/MLAP in both patients ex-

TABLE IV
Left Heart Catheterization Data

Patient	A wave	Z point	V wave	MLAP	Pressure rise in diastasis	RY/ MLAP	Y descent/ 0.1 sec/ MLAP	V/A	Left ventricular pressure S/D
Group I									
ES	4	3	4	14	0	14.8	2.42	1.1	111/3
MG	23	21	45	22	+	12.8	1.34	1.9	Not entered
GB	(AF)	12	27	17	+	4.7	0.71	(AF)	Not entered
LG	(AF)	16	28	20	+	2.7	0.66	(AF)	200/14
AE	22	17	44	26	0	8.9	0.96	2.0	Not entered
AP	10	9	17	7	0	13.3	1.39	1.7	90/9
WB	16	16	16	13	0	4.2	0.33	1.0	91/-
KS	(AF)	22	42	17	+	14.4	1.78	(AF)	138/21
FM	(AF)	17	34	23	+	4.9	0.61	(AF)	125/-
LMc*	38	35	58	36	0	8.4	0.75	1.5	168/33
LB	23	22	40	29	0	5.9	0.66	1.7	Not entered
LJ	(AF)	25	47	35	+	7.6	0.68	(AF)	Not entered
BS	(AF)	10	34	14	+	11.4	1.81	2.0	109/8.5
Group II									
FT	(AF)	22	87	38	+	14.7	1.68	(AF)	198/23
DS	(AF)	12	35	23	+	11.6	1.04	(AF)	Not entered
AW*	(AF)	20	49	33	+	6.6	0.64	(AF)	
RZ	(AF)	20	57	24	+	7.6	1.50	(AF)	110/19
AA	20	18	52	24	+	12.6	1.62	2.6	91/23
LF	(AF)	19	40	22	+	5.6	0.87	(AF)	Not entered
HT*	41	33	55	34	+	8.5	0.68	1.6	120/33
WC	28	25	49	33	0	17.6	1.10	1.7	Not entered
RH	10.8	7	44	20	0	15.2	1.76	3.9	146/9
BM	(AF)	23	42	27	+	4.7	0.92	(AF)	120/20

All pressures in mm Hg. AF = atrial fibrillation. MLAP = mean left atrial pressure. Pressure or absence of pressure rise during diastasis indicated by "+" and "0," respectively. In patients B. M. and R. Z. left ventricular pressures were measured at operation only. In patients W. B. and F. M. left ventricular end diastolic pressure could not be measured with precision because of possible baseline errors but absence of pressure gradient between left atrium and left ventricle was adequately demonstrated.

ceeded 4.0, but the other two ratios were not diagnostic. In all three patients an intravenous infusion of norepinephrine was administered while left atrial pressure was recorded. This was done in order to increase the resistance to ventricular discharge and resulted in a striking increase in the height of the V wave in all three left atrial pressure tracings (Fig. 1). This type of response has not been noted in patients with pure mitral stenosis or in dogs without mitral valve lesions.[35]

Diastasis: This phase of diastole immediately preceding atrial contraction during which atrial pressure normally rises has been observed to be absent in patients with mitral stenosis.[21,32,36,37] Fifteen of the 23 patients in this series exhibited diastasis. In the remaining eight patients, the heart rate exceeded 100 and tachycardia could have masked this phase. The presence of diastasis in the left atrial pressure pulse is therefore considered to be of value in excluding hemodynamically significant mitral stenosis.

Left Ventricular End Diastolic Pressure: Normal left ventricular end diastolic pressures have been reported in patients with pure mitral insufficiency.[13,20,38] It was therefore of interest to observe the high incidence of markedly elevated left ventricular end diastolic and left atrial "Z point"[39] pressures. In pure mitral insuffi-

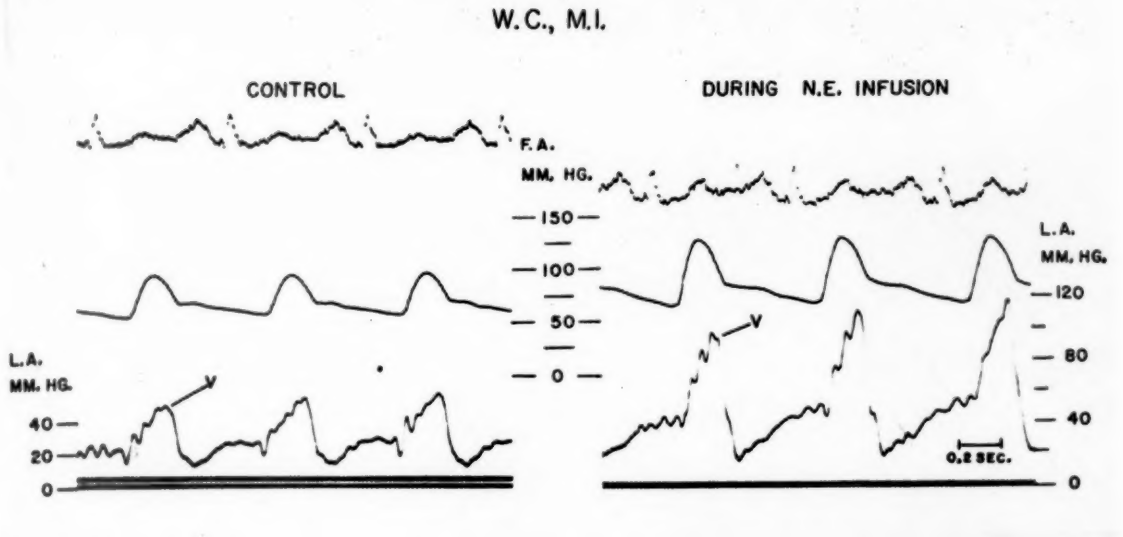

Fig. 1. Left atrial (L.A.) and femoral artery (F.A.) pressures recorded simultaneously in a patient with pure mitral insufficiency. The control observations on the left may be contrasted with the observations during norepinephrine infusion. Striking elevation of the atrial V wave occurs as arterial pressure rises. Diastasis is evident in both atrial tracings.

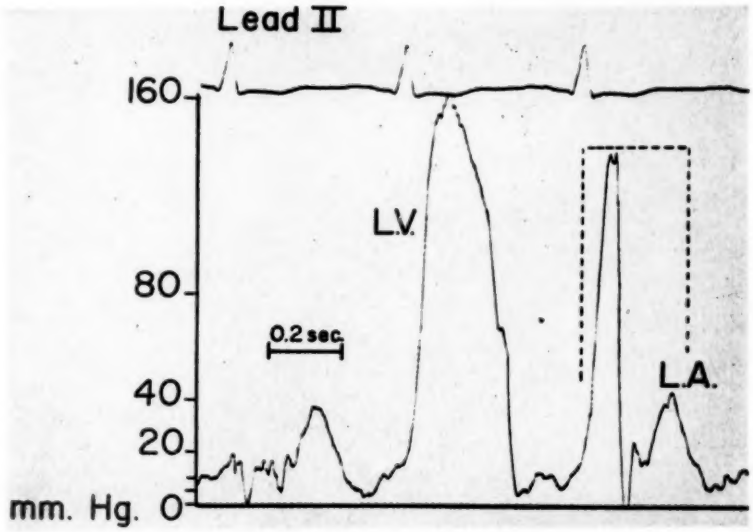

Fig. 2. Left atrial (L.A.) and left ventricular (L.V.) pressure tracings obtained at transbronchial left heart catheterization. Without manipulation, the catheter is washed in and out of the ventricle. The third complex, bracketed, consists of a ventricular tracing during early systole but an atrial one in late systole as the catheter is carried by the regurgitant jet.

ciency the atrial Z point pressure is equal to ventricular end diastolic pressure. Seventeen of the 23 patients had left atrial Z point pressures exceeding 15 mm Hg, and seven of the ten left ventricular end diastolic pressures exceeded this value (Fig. 2). It should be noted that the greatest elevations in left ventricular end diastolic and left atrial Z point pressures were

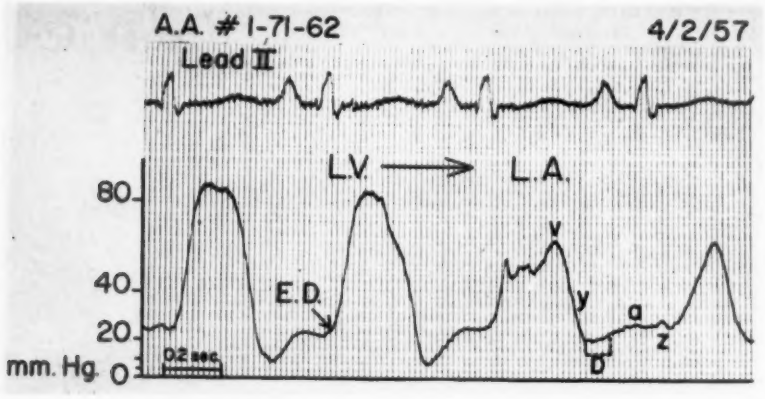

Fig. 3. Left ventricular (L.V.) and left atrial (L.A.) pressures recorded as the catheter is withdrawn across the mitral valve. There is no diastolic gradient between left atrium and left ventricle. The left ventricular end diastolic (E.D.) and left atrial Z point (Z) pressures are elevated. The period of diastasis (D) is indicated.

observed in two of the patients with associated systemic hypertension.

When left heart catheterization is performed with a flexible catheter in patients with mitral insufficiency, left ventricular catheterization is often difficult. The catheter may not enter the ventricle or may enter in diastole, only to be carried back into the atrium by the systolic regurgitant jet. The pressure recordings in these circumstances may show alternate atrial and ventricular contours, or a ventricular contour in diastole and early systole and an atrial V wave late in the same systole (Fig. 3). This "washing phenomenon" is characteristic of mitral insufficiency.[20,21]

Pressure Tracings at Operation: Simultaneous left atrial and left ventricular pressures were recorded at operation in five patients. Wiggers and Feil obtained such tracings in dogs following the production of acute mitral insufficiency,[40] and the similarity of those experimental records to the ones obtained in patients is striking. The studies of Wiggers and Feil indicated that little regurgitation occurs during isometric contraction, presumably because its brief duration does not permit blood inertia to be overcome. Subsequently, during ejection, the large pressure gradient between left ventricle and left atrium results in backward flow which continues into protodiastole and isometric relaxation, since the pressure gradient persists during these periods. The five tracings obtained at operation (Fig. 4) were similar. There was little rise in left atrial pressure during isometric contraction. The pressure then rose rapidly reaching its peak during late ejection and slightly exceeded left ventricular pressure during the Y descent. An abnormally rapid fall in ventricular pressure was noted during late ejection, coincident with the rise of the atrial V wave. All five operative tracings and five of the records obtained at left heart catheterization demonstrated this phenomenon. This contour was described by Davila[41] and has

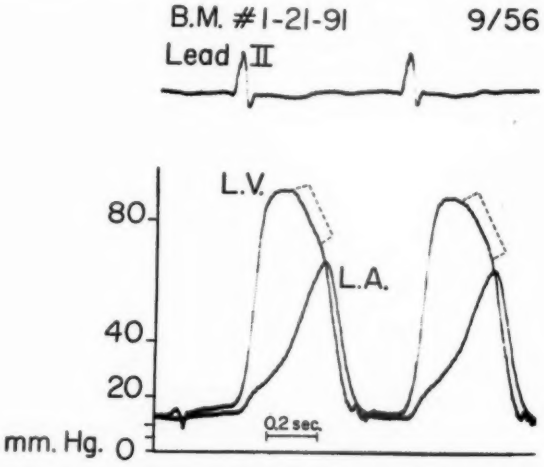

Fig. 4. Simultaneous left atrial and left ventricular pressures recorded at operation. End diastolic pressures are elevated in both chambers; there is no diastolic gradient. The abnormal portion of the ventricular pressure pulse is indicated by the brackets.

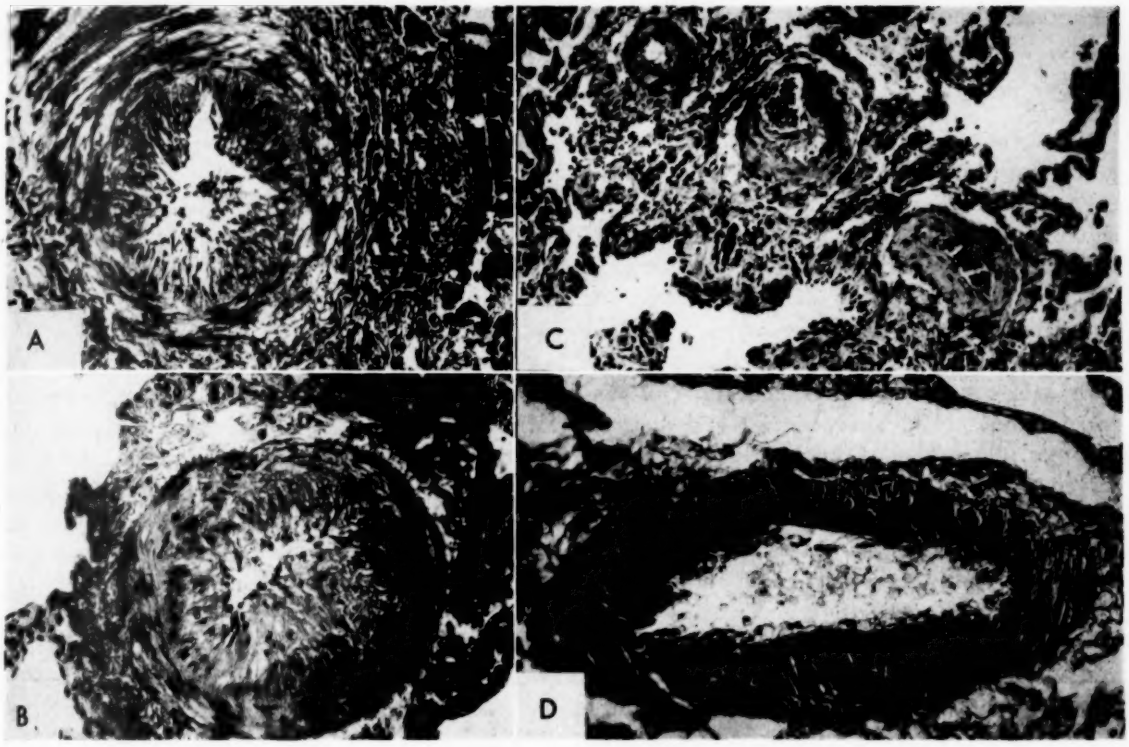

Fig. 5. Photomicrographs of the lungs, H and E stain. Magnifications: A, B, D × 205, C × 145. Pulmonary artery pressures (P.A.) in mm Hg, pulmonary artery resistance (P.A.R.) in dynes sec cm^{-5}. A = Patient R. Z.: P.A. = 61/25, P.A.R. = 729. B = Patient R. H.: P.A. = 84/36. C = Patient A. A.: P.A. = 64/42, P.A.R. = 798. D = Patient A. W.: P.A. = 59/24, P.A.R. = 250. Intimal proliferation is marked in Figures A and B, while medial hypertrophy is striking in Figures C and D.

been attributed to inability of the ventricle to maintain ejection pressure during the period when reverse mitral flow is maximal.

PATHOLOGIC STUDIES

Pulmonary vascular lesions have been infrequently described as an accompaniment of pure mitral insufficiency, although changes consisting of intimal thickening and hyperplastic arteriolar sclerosis are common with mitral stenosis. Most authors have attributed such vascular alterations to increased pulmonary venous pressure and stasis,[42,43] although others have postulated the occurrence of rheumatic arteritis in the lungs.[44]

Becker *et al.*[45] reported two patients with pure mitral insufficiency who had pulmonary vascular changes identical to those found with mitral stenosis. In one instance mitral insufficiency had resulted from traumatic rupture of a valve leaflet, and in the other had followed an attack of bacterial endocarditis. Burchell and Edwards reported an additional patient with chronic mitral insufficiency and associated pulmonary vascular lesions.[7]

In four patients of the present series lung biopsies or postmortem sections were available for histologic study. All of these patients had pulmonary hypertension, and one had associated systemic hypertension. Microscopic sections in all instances revealed medial hypertrophy, sclerosis, and intimal thickening of the pulmonary vessels, particularly the arterioles (Fig. 5). These changes were comparable to the most severe alterations seen with mitral stenosis. Pulmonary arteriolar resistance was markedly elevated in two of these patients, and a large gradient across the pulmonary vascular bed was present in a third. This finding was of interest in view of reports describing an irregular correlation between the pulmonary arteriolar resistance and the severity of the

pulmonary vascular changes in patients with mitral stenosis.[46,47]

Comment

In recent acute experiments[48] metered mitral regurgitant flows of more than twice resting cardiac outputs were induced in dogs. Only slight elevations of the mean left atrial and left ventricular filling pressures were noted, and minimal depression of the effective left ventricular function curve[49] occurred. In other experiments when ventricular filling pressures were held constant and, in the absence of ventricular tone changes, ventricular end diastolic volumes also remained unchanged, it was observed that total left ventricular output could be doubled by increasing mitral regurgitant flow. These findings suggest that increased systolic emptying represents an important compensatory mechanism in mitral regurgitation. It was also observed that a higher left ventricular end diastolic pressure was required for the expulsion of a given volume of blood through the aortic valve than through the regurgitant pathway. It was noted that the extent to which left atrial pressure was elevated as a result of any given mitral regurgitant flow was determined by the filling pressure prior to the induction of regurgitation and, therefore, on the particular ventricular function curve which applied at that time.[49]

It is evident that many of the patients described in this report had severe mitral regurgitation, elevated left ventricular end diastolic pressures, pulmonary hypertension, and right ventricular failure. In light of the experiments described above, the pathogenesis of this clinical picture may be postulated as follows: Large regurgitant flows may exist without striking elevations of left ventricular end diastolic pressure or left atrial mean pressure if myocardial contractility is unimpaired. However, ventricular function may be compromised by processes such as rheumatic carditis, by altered structure of contractile proteins accompanying an increased myocardial burden,[50] or by the existence of hypertension or aortic valve disease. In these circumstances adequate forward cardiac output can be maintained only by elevation of ventricular end diastolic pressure. The large regurgitant flow then results in further elevation of left atrial mean pressure, this in turn may be responsible for the development of increased pulmonary vascular resistance and anatomic changes in the pulmonary vascular bed.[51] The combination of elevated atrial pressure and pulmonary vascular obstruction is responsible for right ventricular systolic hypertension. Thus, the right ventricle is subjected to an increased pressure load, in contrast to the burden of increased flow imposed upon the left ventricle. A different myocardial response to flow and pressure has been established,[52,53] and may account for the predominance of right ventricular failure in many of these patients. It may be noted that, with one exception (R. H.), all patients with pulmonary hypertension in the present series also had an abnormally elevated left ventricular filling pressure.

Although White and others[54,55] have emphasized that severe mitral insufficiency exerts a greater strain on the myocardium and results in a shorter life expectancy than mitral stenosis, until recently many authors have described it as relatively benign with pulmonary hypertension occurring uncommonly and late in the disease;[22,23] even then pulmonary hypertension has sometimes been attributed to supervening mitral stenosis.[23] In this connection, the course of a patient transferred to this clinic following operation is of interest. During mitral commissurotomy severe mitral insufficiency had been produced inadvertently, thus abruptly substituting this lesion for mitral stenosis. She developed an elevated left ventricular end diastolic pressure, pulmonary hypertension, electrocardiographic evidence of right ventricular hypertrophy and intractable right heart failure.

The surgical treatment of mitral insufficiency has been the subject of intense study in many laboratories, and a number of operative procedures have been devised. The results of closed methods for correction of mitral insufficiency have, in this clinic, been disappointing. Recent experiences with the treatment of mitral insufficiency by direct vision of the leaflets and annulus have been encouraging, however. The valve has been exposed by left

atriotomy during complete cardiopulmonary by-pass utilizing a modified Melrose pump-oxygenator. In the patients operated upon thus far, satisfactory correction of the anatomic lesion has been possible, and the hemodynamic results have been good. Further evaluation of this technic in patients far advanced in their course seems justified. However, in the selection of patients for operation, the relatively slow progression of the disease in most patients with mitral insufficiency must be borne in mind.

Summary

The clinical and hemodynamic findings in 23 patients with pure mitral insufficiency are described. Electrocardiographic, roentgenographic and clinical features in the ten patients with pulmonary hypertension are contrasted with findings in the patients without pulmonary hypertension. In the former group pulmonary vascular resistance was elevated, and clinical evidence of right heart failure was frequently present. In general, marked fatigability was noted in patients with abnormally low resting cardiac outputs.

The left atrial pressure pulse contour was characteristic in 20 patients; similar changes in the left atrial pressure contour occurred in the remaining three patients following the infusion of norepinephrine. Left atrial pressure contour analysis proved to be of considerably greater diagnostic value than analysis of the pulmonary capillary wedge pressure tracing. Left atrial Z point pressures were significantly elevated in 17 of the 23 patients and left ventricular end diastolic pressures were elevated in seven of 12 patients. Histologic examination of the lungs in four patients with pulmonary hypertension showed extensive proliferative changes in the pulmonary vasculature.

The possible interrelationships between mitral regurgitant flow and left ventricular function in the production of pulmonary hypertension and right heart failure are discussed.

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Hemodynamic Methods for Differentiation of Mitral Stenosis and Regurgitation*

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SINCE a fully satisfactory operation for the treatment of mitral regurgitation is still lacking, surgical exploration of patients whose predominant lesion is mitral regurgitation may needlessly endanger their lives by subjecting them to the stresses of operation. For this reason, considerable effort has been directed by investigators in cardiovascular research toward the problem of differentiating handicapped patients whose predominant mitral valvular lesion is that of significant stenosis and who are, therefore, candidates for surgical intervention, from those whose predominant mitral lesion is regurgitation. While the clinical findings and the results of routine laboratory studies in classic cases of mitral stenosis and of mitral regurgitation are a sufficient basis for recommending or withholding surgical treatment, determination of the hemodynamically predominant lesion in patients presenting evidence of the presence of combined stenosis and regurgitation may pose a perplexing problem. It is in these cases that the clinician not infrequently seeks assistance from the physiologic laboratory. In this regard, it should be pointed out that in rheumatic mitral valvular disease, by far the commonest form of mitral disease, some degree of stenosis is always found at necropsy, even in persons considered at surgery to have "free regurgitation."[1]

PRESSURE-PULSE CONTOURS

The first portion of this paper will deal with data derived from analysis of pressure-pulse contours. The chronologic evolution of the analysis of pressure pulses with regard to mitral valvular disease will be followed. A description of the various waves comprising the left atrial pressure pulse, along with a brief explanation as to the probable cause of these waves, will serve as a starting point for this discussion.

Normal Left Atrial Pressure Pulse: The left atrial pressure pulse recorded directly during catheterization of the left side of the heart in mitral stenosis (Fig. 1) can be used for this purpose since, except for the increased level of pressure produced by this disease, the contour of the various waves making up the left atrial pulse is approximately similar to the normal. The terminology to be used in describing this pressure pulse in its relation to the cardiac cycle is that of Mackenzie[2,3] and Wiggers[4] and is similar to that used in the description of the peripheral venous pulse. The first positive wave, the A wave, begins shortly after the onset of the P wave of the electrocardiogram and represents an increase in left atrial pressure due to atrial contraction. It is usually followed by a small dip in pressure, the Z point,[5] just prior to the onset of ventricular systole and generally believed to be caused by relaxation of the atrium. The second positive wave, the C wave, appears shortly after the onset of ventricular contraction and is believed to result from closure of the mitral valve, with pushing back into the atrium of the small volume of blood contained between the leaflets, as well as from bulging of the leaflets into the left atrium, thus encroaching on its cavity. A second and larger dip in atrial pressure, the X wave, follows, and this is generally believed to result from the drawing down of the

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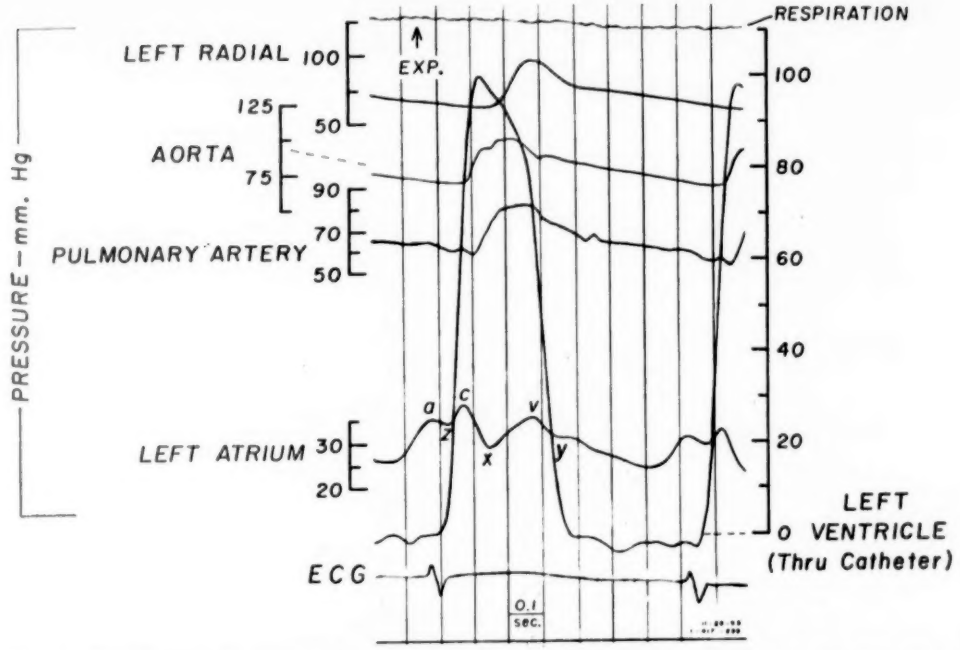

Fig. 1. Simultaneously recorded pressure pulses from various vessels and cardiac chambers in a 49-year-old man with "pure" mitral stenosis (operative diagnosis). The individual waves contained in the usual left atrial pressure pulse are labeled; for the explanation of these symbols, see text. The camera speed in this and Figure 2 was 150 mm per sec.

atrioventricular septum by the contracting ventricle enlarging the atrial cavity and thus producing a decrease in left atrial pressure. The explanation of Ankeny and co-workers,[6] who, like Mackenzie, ascribed the X wave to atrial relaxation, does not appear convincing. During the time that the left ventricle is ejecting blood into the aorta, the mitral valve being closed, continued inflow of blood into the left atrium produces the third positive wave, the V wave, whose peak occurs in protodiastole. The atrial pressure then decreases rapidly to the Y point. This decrease in pressure at the onset of diastole, the "Y descent," is due to the opening of the mitral valve and flow of atrial blood into the ventricle. It should be pointed out that this Y descent is more gradual in the example of mitral stenosis shown than is the case under normal conditions.

Left Atrial Pressure Pulse in Mitral Disease: The left atrial pressure pulse in mitral stenosis, in which the mitral valve obstructs the outflow from the left atrium, is characterized by increase of the general level of left atrial pressure. The other major alteration in contour, as just pointed out, is the more gradual descent of the V wave (Y descent) after the mitral valve opens, which is suggestive of resistance to flow across the valve.[7]

Figure 2 shows a comparison of simultaneously recorded pressure-pulse contours in a case of "pure" mitral stenosis with those recorded in a case of "pure" mitral regurgitation (nonrheumatic with ruptured chordae tendineae) and in a case in which a rheumatic combined regurgitant and stenotic mitral lesion was present. Note the absence of an A wave in the left atrial pulses in the two patients with mitral regurgitation; this absence is caused by lack of a coordinated atrial contraction due to atrial fibrillation. The left atrial pressure pulse in the patient with "pure" mitral regurgitation shows the typical characteristics that can be used as a basis for differentiation of patients with severe regurgitation from those with severe mitral stenosis. In contrast to the left atrial pulse recorded in the patient with "pure" mitral stenosis, these characteristics are as follows: (1) a high peaked V wave is present; (2) there is no apparent C wave, since the trough, or X wave,

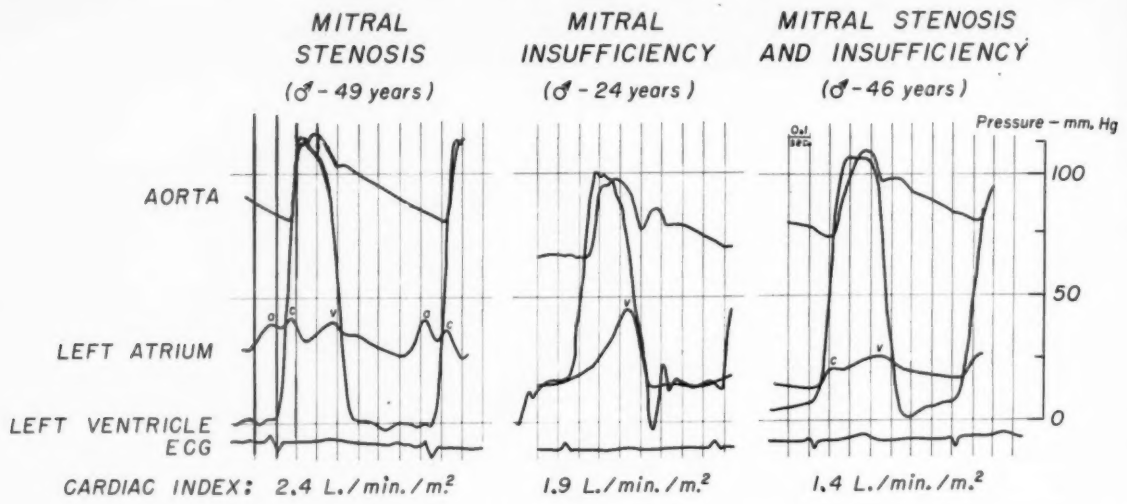

Fig. 2. Simultaneously recorded left atrial, left ventricular, and aortic pressure pulses (redrawn to identical pressure scale), showing recordings from a 49-year-old man with "pure" mitral stenosis (left panel), a 24-year-old man with "pure" mitral regurgitation (middle panel) and a 46-year-old man with combined mitral stenosis and regurgitation (right panel). The diagnosis in each patient was confirmed by surgical findings. Note the characteristic differences in contours of the left atrial pulses recorded in "pure" stenosis and in "pure" regurgitation and the partial fusion of these differences in the patient with combined stenosis and regurgitation. For discussion, see text.

between the C and V waves is absent; (3) if the C wave could be distinguished at the beginning of ventricular systole, its amplitude would be far exceeded by the V wave; (4) there is a rapid descent of the V wave at the termination of ventricular systole. These typical changes in contour, along with the absence of a pressure gradient in diastole, make the diagnosis of severe "pure" regurgitation a certainty in this patient on the basis of simple inspection of these pressure tracings alone.

In contrast, in the patient found at operation to have both mitral stenosis and regurgitation (Fig. 2, right), the diastolic pressure gradient across the valve makes certain the presence of stenosis but the degree of regurgitation is uncertain. The moderately prominent V wave and diminished X wave suggest the presence of some regurgitation, while the gradual Y descent suggests the presence of some stenosis. However, despite the considerable pressure gradient between the left atrium and ventricle maintained throughout diastole, the severity of the mitral stenosis cannot be assessed accurately since, in the presence of significant regurgitation, the flow through the mitral valve during diastole cannot be measured with accuracy in man by presently available technics. The problem, therefore, is to determine what can be accomplished in developing quantitative measurements of the alterations in contour of the left atrial pulse produced by mitral regurgitation, and how accurately these measurements will distinguish between patients with predominant mitral stenosis and those with predominant regurgitation.

PULMONARY ARTERY WEDGE PRESSURE

The analysis of the pulmonary artery "wedge" pressure pulse permitted the first objective, although indirect, estimation of the degree of obstruction to forward flow presented by the diseased mitral valve in man.[8–10] The wedge pressure in the pulmonary artery is a venous type of pressure recorded via a right-heart catheter that has been passed via a pulmonary artery as far as it will go out into the peripheral portion of the lung. Considerable evidence has been presented indicating that this pulmonary artery wedge pressure, in most instances, corresponds closely to the left atrial pressure in both magnitude and contour.[11–15] Various workers have attempted to differentiate patients with mitral valvular disease whose predominant lesion was stenosis from

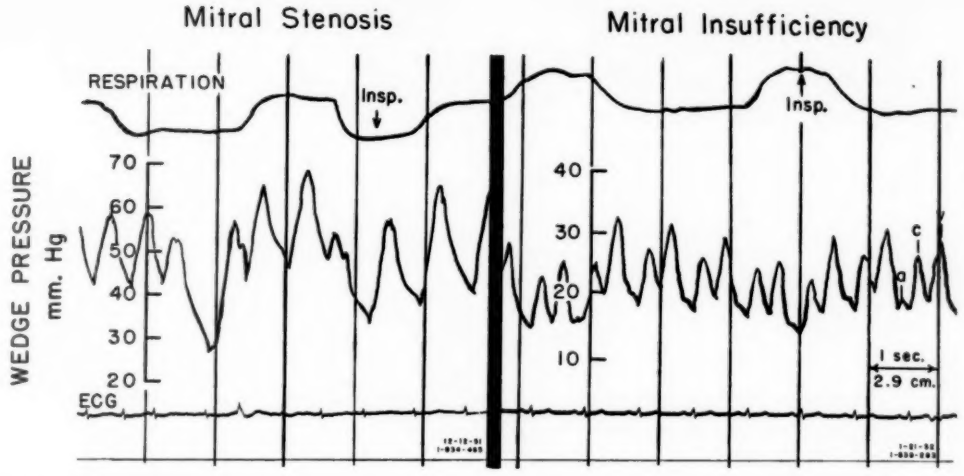

Fig. 3. Comparison of pulmonary artery wedge pressure-pulse contours in a patient with mitral stenosis (left panel) and a patient with mitral regurgitation (right panel). The diagnoses were confirmed at operation. Note that, contrary to what has been described as typical of pulmonary artery wedge or left atrial pulse contours in patients with mitral stenosis and mitral regurgitation, no clearly defined C wave is distinguishable in the patient with mitral stenosis (who also had atrial fibrillation), whereas a clearly defined C wave is seen in the patient with mitral regurgitation. Note the tall peaked V waves in the patient with mitral stenosis.

those whose predominant lesion was regurgitation using this indirect left atrial pressure pulse.[16–20] Since the regurgitant or V wave occurs during ventricular systole, most workers confined their attention to the systolic portion of the pulmonary artery wedge pressure pulse. Attempts to utilize the magnitude of the V wave alone as a means of differentiating mitral stenosis from mitral regurgitation have not been uniformly successful (Fig. 3).

Allison and Linden,[21] using directly recorded left atrial pressures, related the ratio of the pressure difference between the peak of the V wave and the Z point to the peak V wave pressure to differentiate patients with stenosis from those with regurgitation and reported a correct diagnosis in 59 of 61 patients. Owen and Wood,[7] on the basis of the difference that would be expected in obstruction to the forward flow of blood from the left atrium by a stenotic as compared to a regurgitant mitral valve, utilized the rate of descent of the V wave, that is, the early diastolic portion of the wedge pressure pulse, to differentiate between these lesions. Using the ratio of the rate of descent of the V wave to the height of the preceding V wave, they reported an excellent discrimination between cases of stenosis and cases of regurgitation. Connolly and Wood,[20] utilizing pulmonary artery wedge pressure pulses, were unable to confirm the efficacy of these methods in the differentiation between these two conditions in their series of patients (Fig. 4).

Connolly and Wood did find close correlation between the average peak V wave pressure and the mean pressure recorded from the wedge position when the diagnosis, based on palpation at operation, was "pure" mitral stenosis. At equivalent increases of mean pulmonary artery wedge pressure, the peak V wave pressure was significantly greater in patients with mitral regurgitation than it was in patients with mitral stenosis (Fig. 5). When the mean pulmonary artery wedge pressure exceeded 20 mm of mercury, no overlap was encountered in the relationship of the peak V wave pressure to the mean wedge pressure in their series of 20 patients with severe mitral regurgitation and 20 patients with "pure" mitral stenosis. Some aid in distinguishing patients with milder degrees of mitral disease was obtained by recording pulmonary artery wedge pressures during the period of increased pressure produced by exercise. Subsequent experience with this method of distinguishing predominant mitral regurgitation from predominant stenosis has confirmed its value.

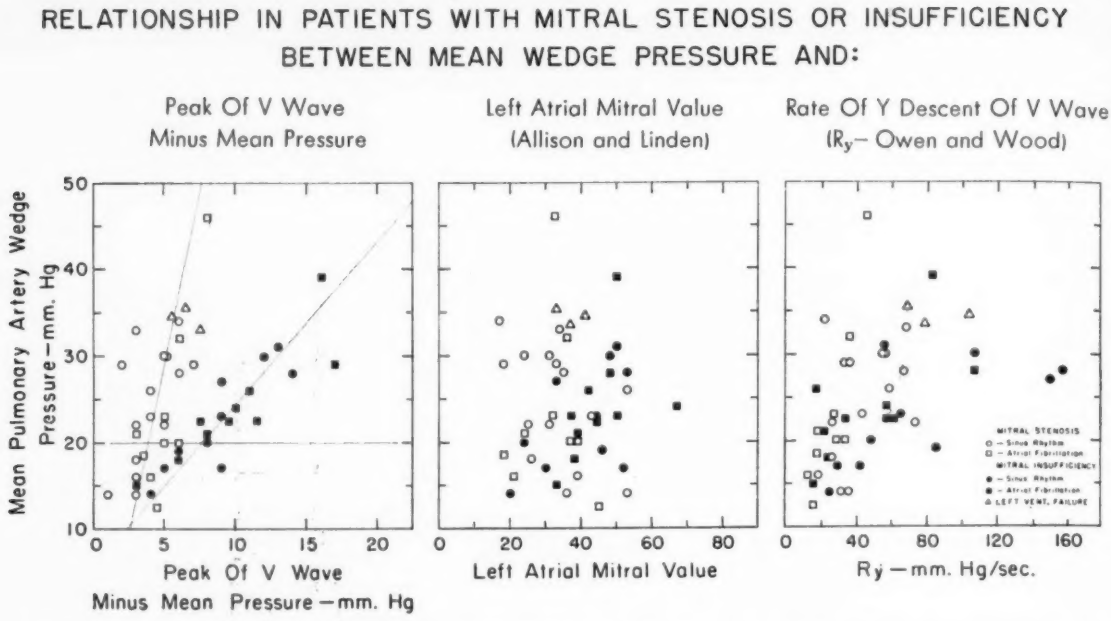
RELATIONSHIP IN PATIENTS WITH MITRAL STENOSIS OR INSUFFICIENCY BETWEEN MEAN WEDGE PRESSURE AND:
Peak Of V Wave Minus Mean Pressure
Left Atrial Mitral Value (Allison and Linden)
Rate Of Y Descent Of V Wave (R_y– Owen and Wood)
Mean Pulmonary Artery Wedge Pressure – mm. Hg
Peak Of V Wave Minus Mean Pressure – mm. Hg
Left Atrial Mitral Value
Ry – mm. Hg/sec.
MITRAL STENOSIS
○ – Sinus Rhythm
□ – Atrial Fibrillation
MITRAL INSUFFICIENCY
● – Sinus Rhythm
■ – Atrial Fibrillation
▲ LEFT VENT. FAILURE

Fig. 4. Comparison of three different methods employed for differentiation of mitral regurgitation from mitral stenosis on the basis of pulmonary artery wedge pulse contours. Note that only the left-hand panel shows a clear-cut separation of patients with mitral stenosis from those with mitral regurgitation; in this series of patients, this separation was uniform when the mean wedge pressure exceeded 20 mm of mercury. For discussion, see text.

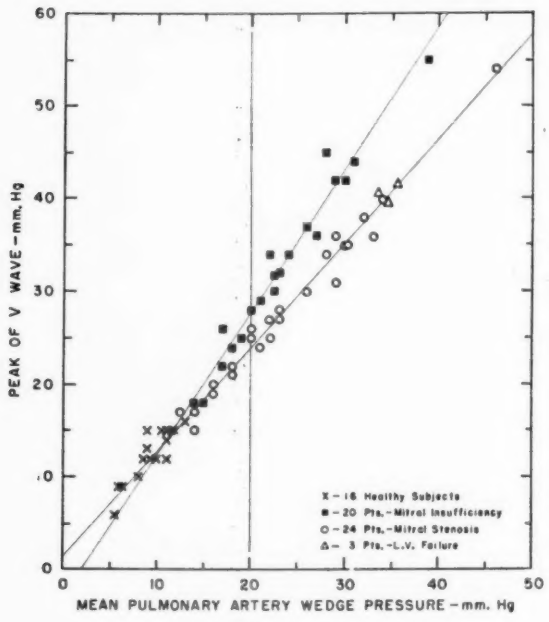
PEAK OF V WAVE – mm. Hg
MEAN PULMONARY ARTERY WEDGE PRESSURE – mm. Hg
X – 16 Healthy Subjects
■ – 20 Pts. – Mitral Insufficiency
○ – 24 Pts. – Mitral Stenosis
△ – 3 Pts. – L.V. Failure

Fig. 5.

Fig. 5. Relationships between average peak V wave pressures and pulmonary artery wedge mean pressures in 24 patients with mitral stenosis, 20 with mitral regurgitation, three with left ventricular failure, and 16 healthy persons. A significant positive correlation between these pressures was obtained in the group with mitral stenosis ($r = 0.99$) and those with mitral regurgitation ($r = 0.98$). The calculated regression equation for the group with mitral stenosis was $Y = 1.1X + 1.4$, and that for the group with mitral regurgitation was $Y = 1.5X + 2.9$ (Y = average peak of V wave and X = mean pulmonary artery wedge pressure in millimeters of mercury). Note that when the pulmonary artery wedge mean pressures exceeded 20 mm of mercury there was no overlap between the patients with mitral stenosis and those with mitral regurgitation and that the patients with left ventricular failure fell in the group with mitral stenosis.

Occasional patients with mixed lesions of the mitral valve have been encountered, however, in whom conflicting results have been obtained[22] (Fig. 6).

LEFT-HEART CATHETERIZATION

Inability to obtain uniform differentiation of patients with predominant regurgitation from those with predominant stenosis on the basis of pulmonary artery wedge pressure pulses led to the development of methods for puncture of the left atrium in man, with the chief objective in mind that direct recordings of left atrial pressure would make possible this differentiation with certainty.[23–25] The provision for simultane-

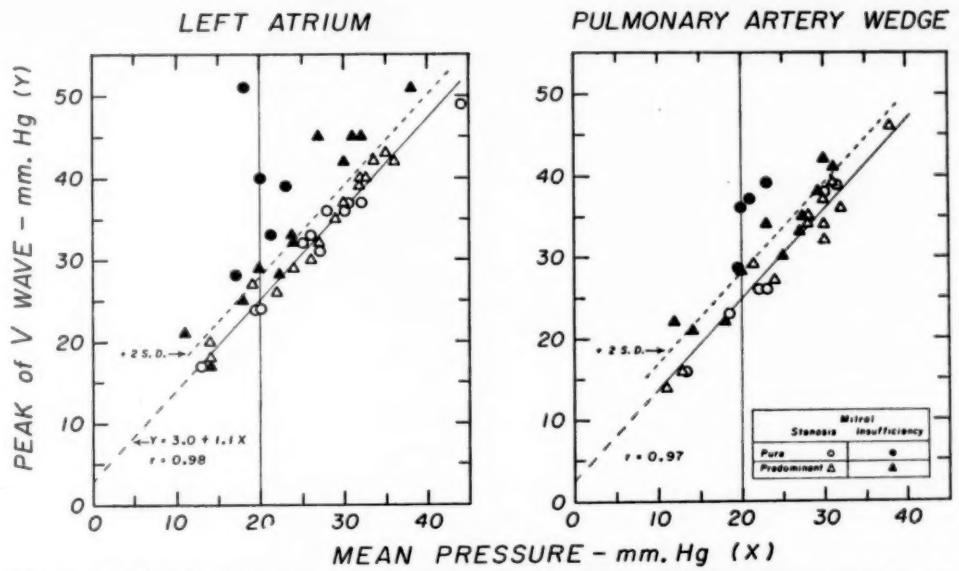

Fig. 6. Relationships between the peak pressure of the V wave and the mean pressure in pulmonary artery wedge pressure tracings (right panel) and directly recorded left atrial pressure tracings (left panel) in 43 patients with mitral valvular disease. Pulmonary artery wedge pressures were obtained in 33 of these patients. The regression line for patients with "pure" and predominant mitral stenosis calculated from the directly recorded left atrial pressures is shown in both panels (solid line). The broken lines represent two standard deviations above the regression line. Note that the same regression line fits both sets of data. When the mean left atrial pressure exceeded 20 mm of mercury, values in only two of the patients with predominant mitral regurgitation fell into the range of values found in patients with predominant mitral stenosis.

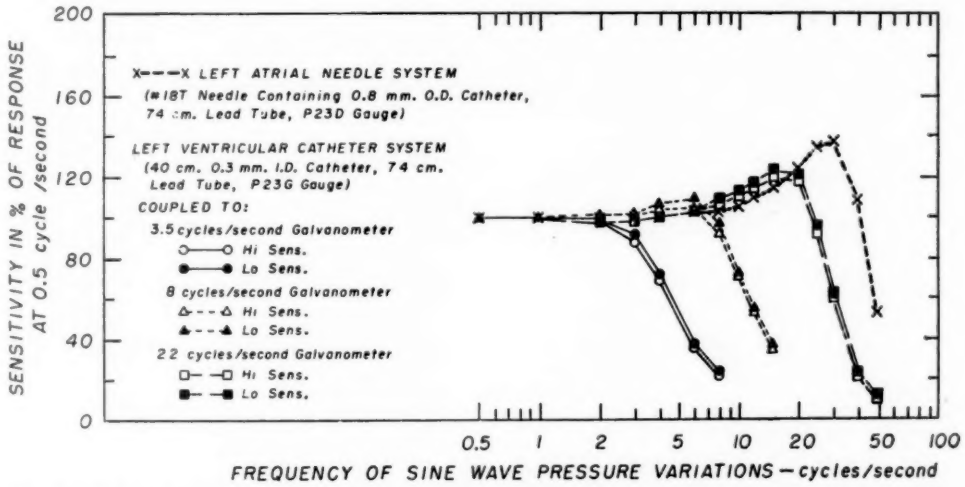
SENSITIVITY IN % OF RESPONSE AT 0.5 cycle /second
X---X LEFT ATRIAL NEEDLE SYSTEM
(#18T Needle Containing 0.8 mm. O.D. Catheter, 74 cm. Lead Tube, P23D Gauge)
LEFT VENTRICULAR CATHETER SYSTEM
(40 cm. 0.3 mm. I.D. Catheter, 74 cm. Lead Tube, P23G Gauge)
COUPLED TO:
3.5 cycles/second Galvanometer
Hi Sens.
Lo Sens.
8 cycles/second Galvanometer
Hi Sens.
Lo Sens.
22 cycles/second Galvanometer
Hi Sens.
Lo Sens.
FREQUENCY OF SINE WAVE PRESSURE VARIATIONS - cycles/second

Fig. 7. Dynamic response of manometer systems used for studying the effect of variation in dynamic response of the manometer system on the left ventricular and left atrial pressure pulses recorded by these different systems. These identical manometer systems were used to record the left ventricular and left atrial pressure pulses shown in Figure 8.

ous recording of the left atrial, left ventricular, aortic and pulmonary arterial pressures, along with blood flow,[26] considerably increased the precision of the measurement obtained. It has been demonstrated that, by proper attention to details of instrumentation,[26–28] left ventricular and left atrial pressure pulses can be recorded accurately and simultaneously through a single

18-gauge needle-catheter assembly (Figs. 7 and 8). This technic is more convenient and probably carries a greater margin of safety than does the more commonly used method of double needle puncture of the left atrium or the use of a large (16-gauge) needle-catheter assembly.

By measurement of the diastolic pressure gradient across the mitral valve along with the blood flow, it has been demonstrated that pure mitral stenosis can be detected and quantitated with considerable accuracy.[29–34] Pure mitral regurgitation also can be demonstrated with acceptable certainty. It was found, however, that the magnitude of the pressure gradient across the mitral valve lost its importance when significant stenosis and regurgitation coexisted, since, in the presence of significant regurgitation, only the net forward flow across the valve can be measured and the actual flow during diastole is unknown. Actually, pressure gradients measured in patients with predominant regurgitation were found fairly commonly to be as high as or in excess of those found in patients with "pure" mitral stenosis (Fig. 9). Therefore, it became necessary to turn attention to the contour of the left atrial pressure pulse in an attempt to find some method of discrimination of these two types of valvular defects.

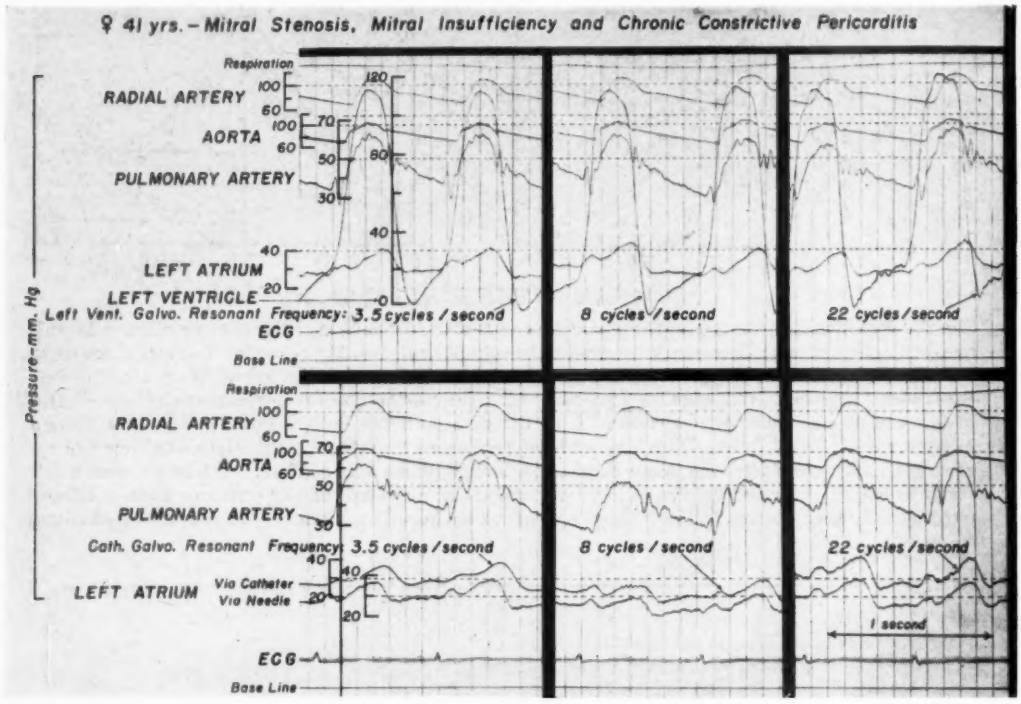

Fig. 8. Effect of variations in the dynamic response of the manometer recording system on the contours of left ventricular (upper panel) and left atrial pressure pulses (lower panel). These pressure recordings were obtained in rapid succession from the same patient with the manometer systems designated 3.5, 8, and 22 cycles per sec, respectively, whose dynamic response curves are shown in Figure 7. Note that the minimal and maximal ventricular pressures recorded by the three systems are not significantly different despite the fact that the range of uniform response to sine-wave pressure variations for these systems ranged from 3.5 to 22 cycles per sec (Fig. 7). The damping and time lag of the pressure pulses recorded by the 3.5-cycle system is more obvious in recordings of the left atrial pressure pulses (lower left panel), although minimal and maximal left atrial pressures are indicated with reasonable accuracy.

No appreciable difference was noted between the left atrial pressure pulses recorded simultaneously by the 22-cycle catheter system and the 40-cycle left atrial needle system (lower right panel). The dynamic response of these two manometer systems is similar to that used routinely for simultaneous recording of left ventricular and left atrial pressures via a single 18-gauge needle assembly introduced percutaneously into the left atrium.[26]

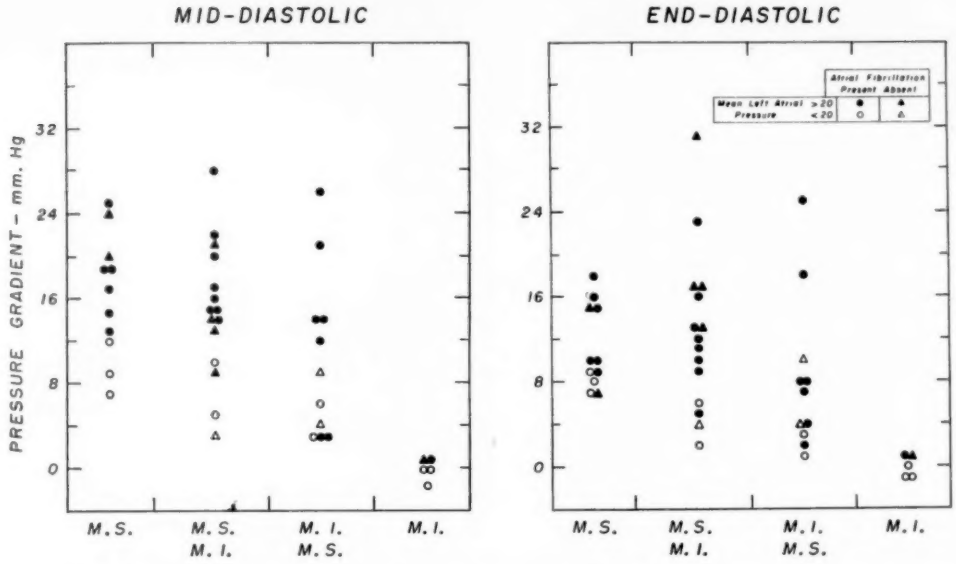

Fig. 9. Relationships between the mid-diastolic and end-diastolic pressure gradient and the degree of regurgitation in 42 patients with mitral valvular disease. The degree of mitral regurgitation is plotted on the abscissa, starting with "pure" mitral stenosis (M.S.) on the left and progressing to predominant mitral stenosis with some regurgitation (M.S., M.I.), then to predominant mitral regurgitation with some stenosis (M.I., M.S.) and finally to "pure" mitral regurgitation (M.I.) on the right. Note that the pressure gradient in patients with predominant regurgitation may be as high as and in some instances even higher than that in patients with pure mitral stenosis.

LEFT ATRIAL PRESSURE PULSES

Careful analysis of the directly recorded left atrial pressure-pulse contours was undertaken in 43 patients studied by simultaneous catheterization of the aorta and the right and left sides of the heart. Left ventricular, left atrial, aortic, radial, and pulmonary arterial pressures, which were simultaneously recorded photokymographically at a paper speed of 150 mm per second, were used in this study.[22] An original recording of these pressures is shown in Figure 1. In all of the 26 patients who had pure or predominant mitral stenosis, the diagnosis was confirmed at operation. In five of the 17 patients who had "pure" or predominant mitral regurgitation, the diagnosis was similarly confirmed at operation; in the remaining 12 patients, who were nonsurgical, the results of clinical and routine laboratory examinations indicated the presence of regurgitation. In addition, dilution curves recorded simultaneously from the left atrium and the radial artery after injections of indicator into the left and right sides of the heart showed the alterations that are considered to be indicative of the presence of hemodynamically significant mitral regurgitation in the proved absence of aortic valvular disease and of an intracardiac left-to-right shunt. These findings were considered to establish the presence of predominant mitral regurgitation with certainty, so that these patients were not offered surgical treatment.

The directly recorded left atrial pressure pulses in this group of 43 patients were analyzed according to the methods already mentioned in study of the pulmonary artery wedge pressures. In addition, the difference between the C wave and V wave pressures, suggested by Kent and co-workers,[35] and the difference between the C wave and X wave pressures, suggested by McMichael and Shillingford,[36] for study of tricuspid regurgitation also were included in this analysis. The results of Kent and associates suggested that slight regurgitation was present when the V wave pressure exceeded that of the C wave by 6 to 8 mm of mercury; when this difference was more than 10 mm, the degree of regurgitation was considered to be severe. The tendency of the X wave of the atrial pulse to dis-

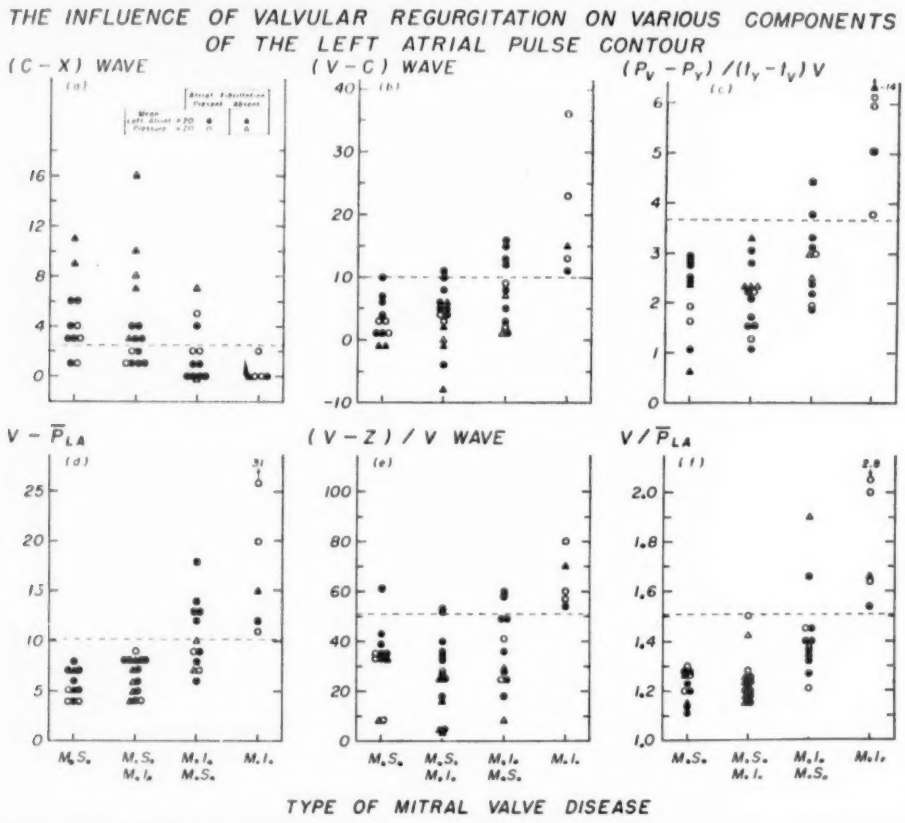
THE INFLUENCE OF VALVULAR REGURGITATION ON VARIOUS COMPONENTS OF THE LEFT ATRIAL PULSE CONTOUR
(C - X) WAVE
(V - C) WAVE
(Py - Ps) / (ty - ts) V
V - P̄LA
(V - Z) / V WAVE
V / P̄LA
M.S.
M.S. M.I.
M.I. M.S.
M.I.
TYPE OF MITRAL VALVE DISEASE

Fig. 10. Relationships in 43 patients with mitral valvular disease between six measurements derived from left atrial pressure pulses and the degree of mitral regurgitation graded as in Figure 9. Panel *a* shows the difference in millimeters of mercury between the peak pressure of the C wave and the pressure of the C-V trough, or the X wave. Panel *b* shows the pressure differences between the peak of the V wave and the peak of the C wave. When a C wave was not present due to absence of the X wave, a point on the left atrial pulse contour corresponding to the period of isometric contraction of the left ventricular contour was chosen. Panel *c* gives the ratio of the Ry descent to the V wave, as suggested by Owen and Wood.[7] The difference in pressure between the peak of the V wave and the base of the Y descent in millimeters of mercury is divided by the difference in time in seconds between these identical points ($t_y - t_v$) and the result is divided by the peak pressure of the V wave. Panel *d* indicates the difference between the peak V wave pressure and the mean left atrial pressure (P_{LA}), as proposed by Connolly and Wood.[20] Panel *e* shows the "left atrial mitral value," as proposed by Allison and Linden.[21] The difference between the peak V wave pressure and the Z point is divided by the peak V wave pressure. This is expressed as a percentage by multiplying the result by 100. Panel *f* shows the ratio of the peak V wave pressure and the mean left atrial pressure.

The dashed lines in each panel are drawn so as to include all of the values obtained from patients with "pure" mitral regurgitation. Note that a correlation is present in every panel but only four panels (*b*, *c*, *d* and *f*) give complete separation of "pure" mitral stenosis and "pure" mitral regurgitation. An overlap of patients with combined valvular disease occurs in every panel. For discussion, see text.

appear in the presence of regurgitation (Fig. 2) has been expressed as the "C minus X wave pressure difference," this value being zero if the X wave is absent.

The results of this analysis of the left atrial pressure-pulse contours are summarized in Figure 10, in which each of six methods suggested for distinguishing mitral stenosis from mitral regurgitation is plotted on the ordinate against the degree of regurgitation on the abscissa. While significant correlation is evident between each of these measurements and the degree of regurgitation judged to be present, considerable overlap occurs, especially in the two middle groups, in

which combined mitral lesions are present. Only four of the six measurements (panels *b*, *c*, *d*, and *f*) actually show a complete separation of the most divergent of the groups, that is, the patients with "pure" stenosis and those with "pure" regurgitation. However, certain abnormalities of the left atrial pressure pulse were found to be fairly characteristic of a particular condition. For example, when the ratio of the rate of the V wave descent to the peak V wave pressure (Owen and Wood[7]) exceeds 3.5 (panel *c*), when the average peak V wave pressure exceeds the mean left atrial pressure by 10 mm of mercury or more (panel *d*), or when the ratio of the peak V wave pressure to the mean left atrial pressure exceeds 1.5 (panel *f*), the presence of severe mitral regurgitation is strongly favored.

Rate of V Wave Descent: The rate of the V wave descent was investigated further as a means of differentiating mitral stenosis and regurgitation. As already noted, Owen and Wood[7] originally recommended that the rate of V wave descent be divided by the peak V wave pressure (Fig. 10, panel *c*). Actually, the use of such a ratio in this series of 43 patients produced no appreciable improvement over the discrimination obtained by use of the V wave descent alone (Fig. 11, left). However, a positive correlation was demonstrated between the mean left atrial pressure and the rate of the V wave descent. Consequently, use of a ratio of the rate of V wave descent to the mean left atrial pressure (Fig. 11, right) improved somewhat the discrimination obtained but an overlap persisted in five of 11 cases of predominant regurgitation with the values obtained in patients with predominant stenosis, as compared to an overlap in nine of the 11 cases when the ratio originally recommended by Owen and Wood was used.

Effect of Atrial Fibrillation: The presence of atrial fibrillation had no apparent effect on the discrimination obtained by the various parameters studied except for the X wave. As previously reported,[6] the X wave was more pronounced in patients with a normal sinus rhythm than it was in those with fibrillation (Fig. 10, panel *a*). This finding has been used as a point in favor of atrial relaxation as the cause of the X wave. However, it is difficult to explain on this basis the presence of an X wave in each of the 26 patients with "pure" or predominant stenosis in this series, only seven of whom had a normal sinus rhythm. In any event, complete absence of the X wave can be regarded as significant evidence of mitral regurgitation since, in the present series, this was found only in patients with "pure" or predominant mitral regurgitation (Fig. 10, panel *a*).

Peak V Wave Pressure: The relationship of the mean left atrial pressure to the peak V wave pressure also was investigated in this series of patients, both from directly recorded left atrial pressure pulses and from the pulses recorded from the pulmonary artery wedge pressure in 33 of these same patients in whom pulmonary artery wedge tracings were obtained during combined catheterization of the right and left sides of the heart (Fig. 6). The close correlation between mean left atrial or wedge pressure and the peak V wave pressure obtained by Connolly and Wood[20] in patients with mitral stenosis was confirmed. The regression equation expressing this relationship obtained by Connolly and Wood was not significantly different from the regression equation calculated from the left atrial or pulmonary artery wedge pressure data obtained in this series of patients.

It is of considerable interest that this correlation is so close (correlation coefficient = 0.98) that, in the absence of mitral regurgitation, the V wave pressure apparently can be calculated from the mean left atrial pressure by means of the regression equation:

V wave peak = 3.0 + 1.1 (mean left atrial pressure) with a standard deviation between measured and calculated values of less than 2 mm of mercury.

It is also of interest that values for the peak V wave and mean left atrial pressure reported from another laboratory[30] fall extremely close to this regression line. The close similarity of the relation of V wave pressure to mean pressure recorded from the wedge position and directly from the left atrium is additional evidence that properly recorded pulmonary artery wedge pressures are a reasonably accurate reflection of left atrial pressure.

Of the parameters of the left atrial pressure

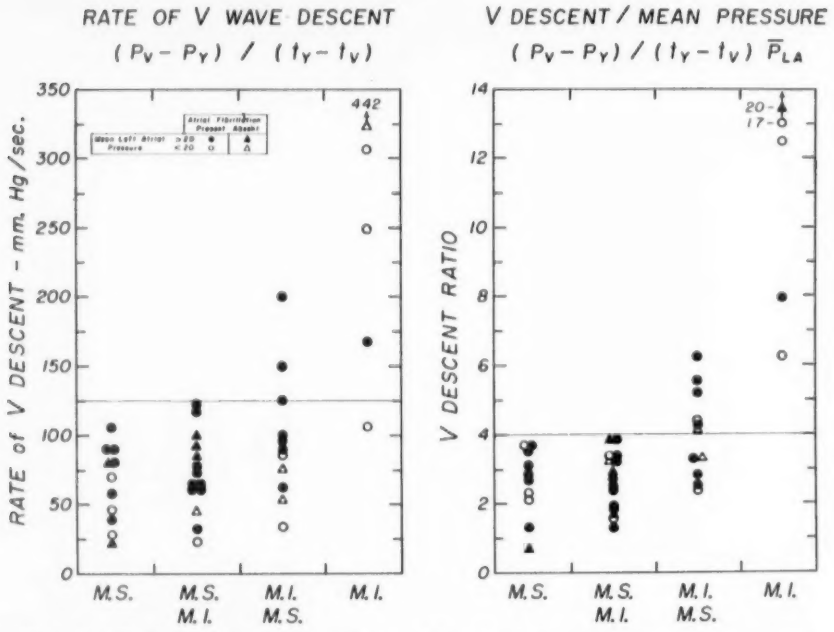

Fig. 11. Relationships in 42 patients with mitral disease between the rate of V wave descent (left panel) and ratio of the V wave descent to the mean left atrial pressure (P_{LA}) (right panel) and the degree of mitral regurgitation. The solid line is drawn across the upper limit of values in patients with predominant stenosis with some regurgitation. Note the improvement in correlation when the rate of V wave descent is divided by the mean left atrial pressure. For discussion, see text.

pulse that were studied, the relationship of the peak V wave pressure to mean left atrial pressure gave the best differentiation between patients with predominant mitral stenosis and those with predominant regurgitation, particularly in those in whom the method is applicable by Connolly and Wood's criterion that the mean left atrial pressure be in excess of 20 mm of mercury. There was no overlap of values from patients with "pure" mitral regurgitation into the area encompassing two standard deviations from the regression lines for patients with "pure" or predominant mitral stenosis for either the left atrial or pulmonary artery wedge data. However, in the 11 patients who had predominant mitral regurgitation associated with significant stenosis, overlap occurred in two and four instances in the left atrial and pulmonary artery wedge pressure data, respectively, from patients with mean left atrial pressures in excess of 20 mm.

Other attempts to attain better discrimination of stenosis and regurgitation from the left atrial pressure pulse have been investigated.

The timing of the instant of the peak V wave pressure in the cardiac cycle has been studied in relation to the presence of mitral regurgitation. The accentuated V wave associated with regurgitation is presumed to be the result of the additive effect of normal filling of the left atrium from the pulmonary veins and of blood regurgitated into the atrium through the mitral valve. Therefore, it might be expected that the peak pressure of the V wave associated with mitral regurgitation would occur in closer relationship to the termination of ventricular systole than would the peak pressure of the V wave associated with normal filling of the left atrium undistorted by regurgitated blood, which is absent when the mitral valve is competent. The average relationships of the Q-T interval of the electrocardiogram to the interval from the Q wave of the electrocardiogram to the peak of the V wave and to the end of ventricular systole were found to be not significantly different in patients with mitral stenosis or regurgitation. However, as might be anticipated, the spread of values for these relationships is much

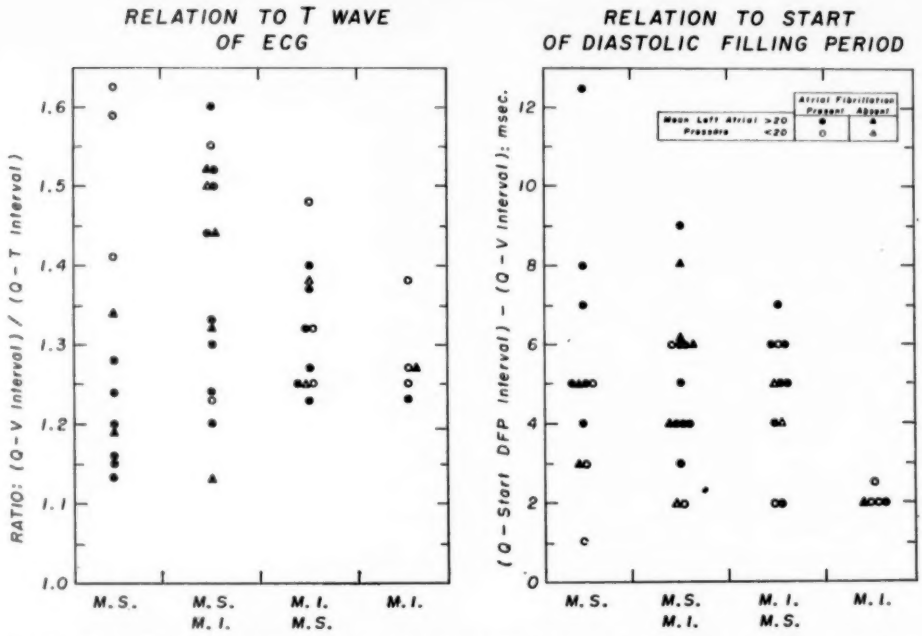

Fig. 12. Relationships in 42 patients with mitral disease of the degree of mitral regurgitation to the ratio of the Q-V wave interval and the Q-T interval of the electrocardiogram (left panel) and the difference between the interval from the Q wave to the start of the diastolic filling period (DFP) and the Q-V wave interval (right panel). Note that no correlation is evident between the time of occurrence of the V wave peak and the degree of regurgitation. However, in patients with "pure" mitral regurgitation, the range of values obtained for the time of occurrence of the V wave peak in relation to the onset of the diastolic filling period is considerably less than the range obtained for patients with mitral stenosis. For discussion, see text.

less in patients with "pure" mitral regurgitation (Fig. 12).

Left Ventricular End-Diastolic Pressure: Since the work load of the left ventricle is unchanged or decreased in the presence of mitral stenosis and greatly increased in the presence of clinically significant mitral regurgitation, it would be logical to expect a higher left ventricular end-diastolic pressure in patients with mitral regurgitation than in those with mitral stenosis. In fact, a positive correlation can be demonstrated between the diastolic pressure in the left ventricle and the degree of mitral regurgitation. However, the wide range of values obtained in patients with various categories of mitral valvular disease minimizes the value of this parameter as a means of differentiating mitral stenosis and regurgitation (Fig. 13).

Since a significant correlation can be demonstrated between many different parameters of the left atrial pulse and the degree of mitral regurgitation (Figs. 10–13), it is logical to assume that multiple-variable analysis using various properly weighted combinations of these parameters might greatly improve the discrimination obtained.[37] However, preliminary attempts along this line have been discouraging. A combination of the rate of V wave descent and the peak V wave-mean left atrial pressure difference, one of the better combinations studied, failed to provide uniform discrimination between patients with predominant stenosis and those with predominant regurgitation (Fig. 14).

Systemic Arterial Pressure Pulses: Since it is logical to presume that the ejection of blood from the left ventricle might differ in a characteristic fashion in patients with severe mitral regurgitation and those with mitral stenosis, the presence of characteristic differences in the contours of pressure pulses recorded from systemic arteries in such patients would not be a surprising finding. Paul Wood[38] has described characteristic differences in peripheral arterial pressure pulses between patients with mitral stenosis and those with regurgitation. However,

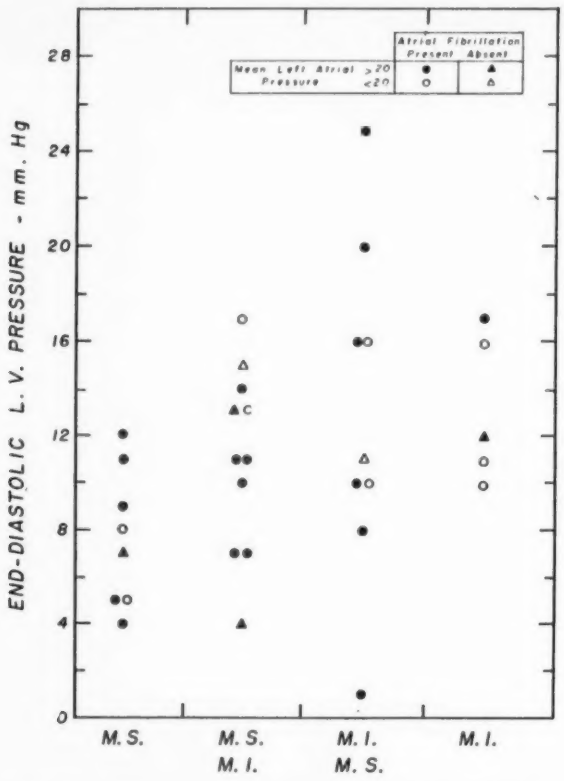

Fig. 13. Relationships in 33 patients with mitral disease of the end-diastolic pressure in the left ventricle to the degree of mitral regurgitation (patients with evidence of aortic valvular disease were excluded in this study). As expected, patients with severe mitral regurgitation tend to have an increased diastolic pressure in the left ventricle. However, considerable overlap occurs in the values obtained from patients with the different categories of mitral valvular disease.

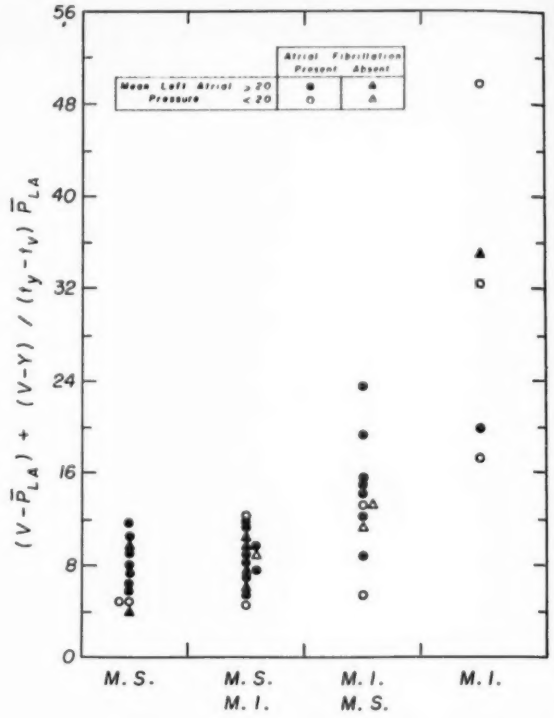

Fig. 14. Relationships in 42 patients with mitral disease of a combination of parameters measured from the left atrial pressure pulse to the degree of mitral regurgitation. Note that this combination of parameters (rate of V wave descent and peak V wave pressure in relation to the mean left atrial pressure [P_{LA}]), which by themselves gave a significant degree of discrimination between stenosis and regurgitation, did not produce a striking improvement in the degree of differentiation over that obtained when these parameters were used individually (Fig. 10).

studies of pressure pulses recorded simultaneously from the aorta and radial artery of such patients carried out by Wright[39] in this laboratory have failed to reveal characteristic differences in systemic arterial pulse contours between such patients.

Summary of the Differentiation of Mitral Stenosis and Regurgitation by Means of Pressure-Pulse Contours: These various studies of pressure pulses recorded from patients with mitral valvular disease show that, in the presence of both stenosis and regurgitation of the mitral valve, completely uniform separation of patients whose predominant defect is stenosis from those with predominant regurgitation was not attained from analysis of pressures and pressure-pulse contours alone. However, these methods are of definite value as an aid in making this distinction in problem cases, since certain abnormalities of the pulse wave practically never occur in the absence of severe regurgitation. Of the methods studied, the analysis relating the peak pressure of the V wave to the mean left atrial pressure gave the best discrimination between patients with predominant mitral stenosis and those with predominant regurgitation.

Indicator-Dilution Curves

Because of the failure to obtain uniform discrimination by means of clinical criteria along with pressure-pulse and blood-flow data, various investigators have turned to a study of indicator-

dilution methods in the hope that the desired degree of diagnostic acumen could be attained.

When an indicator dye is injected suddenly into the circulatory system, it is mixed with and transported by the blood throughout the vascular system in a characteristic manner. A record of its concentration against time during the initial traversal of the circulation is called an "indicator-dilution curve."

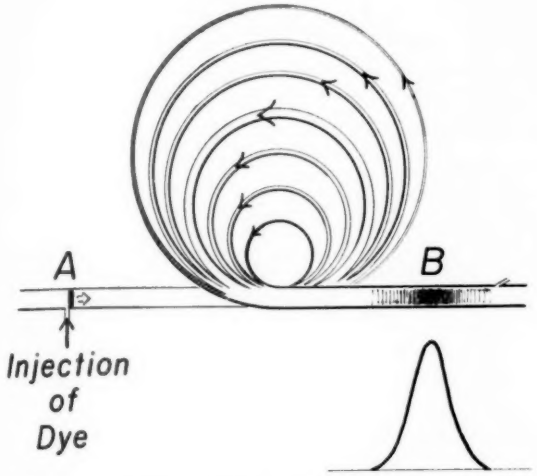

Fig. 15. Diagram illustrating the effect of paths with different traversal times such as would occur in the lungs on the distribution of a miscible substance introduced into a flowing stream at point A and observed at point B. Since some material traverses short pathways, some follows pathways of medium length and some traverses long pathways, the times of arrival at point B will vary, so that the substance will be dispersed along the length of the vessel at B as a concentration-distance curve (illustrated immediately below in the diagram). Laminar flow along a single vessel also produces longitudinal dispersion.[41] If a sample is drawn continuously from a single point, for example, distal to B, then a concentration-time curve is obtained. The duration of the curve on the time axis represents the interval required for the blood in which the indicator is dispersed to pass the sampling site. Dilution curves almost always are recorded as functions of concentration and time.

Figure 15 illustrates diagrammatically how the indicator dye is dispersed during its first passage through a complex circulation, such as in the lungs, after its injection as a single "bolus" into the pulmonary artery, with sampling at a systemic artery. The contour of the resulting dilution curve is determined by the volume-rate of flow through the vascular system, the volume of the vascular system between the injection and sampling sites, the distribution of short and long circulatory pathways through the system [40] and other factors.[41] The importance of dilution curves in cardiovascular physiology can be given proper emphasis by the statement that a recording of the dilution of an indicator during its initial traversal of a circulation provides more information concerning the status of this circulation than does observation of any other single variable. From such a dilution curve one can determine the volume rate of flow through the circulatory system, the volume of the system between injection and sampling sites, the fastest and the mean circulation times through the system, the presence or absence of abnormal circulatory pathways or severely incompetent valves, and a number of other parameters of importance in the circulation.

Typical dilution-curve patterns have been found to be usually associated with various states of the circulatory system in man.[42]

The effect of a striking change in cardiac output can be illustrated by comparing dilution curves recorded immediately before and after manual occlusion of a femoral arteriovenous fistula in an otherwise healthy man (Fig. 16). The bottom curve, with the fistula occluded, is

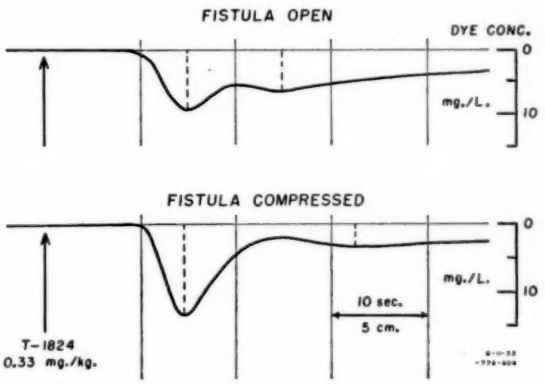

Fig. 16. Dye-dilution curves recorded after injection of dye into the antecubital vein of a 15-year-old boy who had a femoral arteriovenous fistula. The upper curve was recorded with the fistula open and the lower curve was obtained when flow to the fistula was abolished by manual compression. Note the similar appearance times of the two curves, with greatly different peak concentrations and systemic recirculation times (intervals between broken lines). The upper curve reflects the increased cardiac output and the reduced circulation time owing to the rapid flow of blood via the shortened vascular pathway through the fistula.

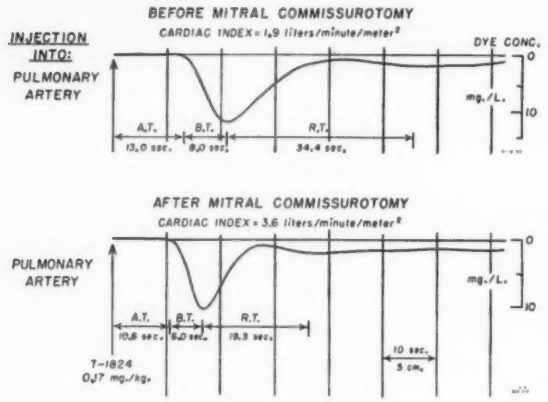

Fig. 17.

Fig. 17. Changes in dilution curves associated with congestive heart failure in a 41-year-old man with mitral stenosis. The dilution curve in the upper panel was recorded before and that in the lower panel six months after a highly successful mitral commissurotomy performed by Dr. J. W. Kirklin. Before relief of the mitral stenosis, the cardiac index was below the range of normal; after commissurotomy, a normal value was attained. The lower curve is of normal contour and the time components (A.T. = appearance time; B.T. = build-up time; R.T. = systemic recirculation time) are within the range of normal values. A feature of the upper curve is the prolongation of the time components seen in patients with reduced cardiac output. In particular, note the dramatic changes in recirculation time (R.T.) from 34.4 sec before operation to 19.3 sec after operation.

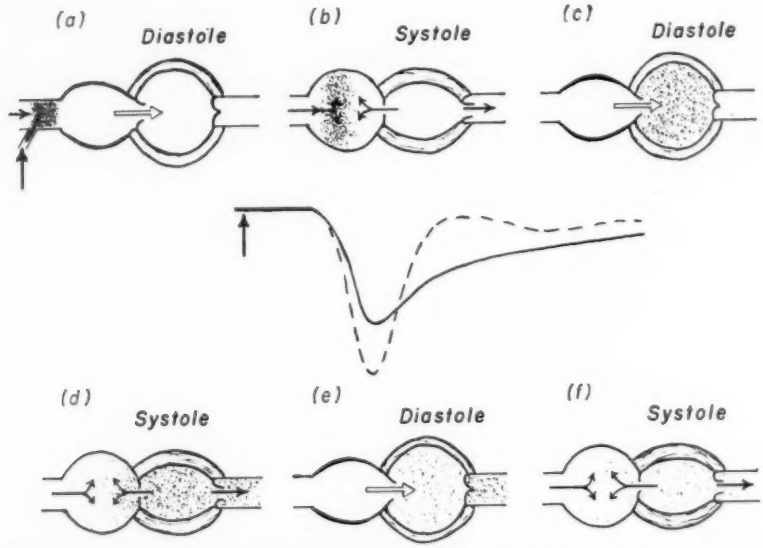

Fig. 18. Diagrammatic illustration of the effect of valvular regurgitation on the passage of an indicator through the cardiac chambers. In the center of the figure are illustrated a normal curve (broken line) and the abnormal (solid line) dilution curve associated with severe valvular regurgitation. Indicator is injected at the inflow to the cardiac chamber (*a*). When it flows into the atrium during the next ventricular systole (*b*), it is diluted by the volume of blood regurgitated through the incompetent valve during systole. The dye-blood mixture then passes into the ventricle during the succeeding diastole (*c*); during the subsequent systole (*d*), a portion of the dye-blood mixture is regurgitated back into the atrium and a portion is ejected forward into the aorta. This process is repeated during successive cardiac cycles (*e* and *f*) so that the time required for the dye to be cleared from the cardiac chambers is greatly prolonged.

completely normal. A downward deflection occurs with increasing concentration of the dye. The second concentration peak is caused by dye recirculating in its second traversal of the systemic circulation. The interval of 18 seconds between the two concentration peaks in the bottom curve is related to the mean systemic circulation time, that is, the average time required for the blood to make a complete traversal of the vascular system. The upper curve, recorded when the fistula was open, shows the effect of an extremely high cardiac output. The amplitude of the curve is reduced because the dye is diluted in a greater volume of blood,

and all the time components are reduced because the velocity of blood flow is increased by the high cardiac output, the systemic recirculation time being decreased by almost 50 per cent.

Figure 17 illustrates the effect of stenotic valvular disease and consequent congestive heart failure by a comparison of dilution curves recorded before and after surgical relief of severe mitral stenosis. The proportionate slowing of all time components of the upper curve results from the low cardiac output and increase in blood volume associated with congestive heart disease. The lower curve from the same patient, recorded after relief of the stenosis, is completely normal.

Cardiac disease due to valvular regurgitation not only causes the changes in flow and volume in the vascular system associated with congestive heart failure but also produces an abnormal flow pattern through the heart, since both forward and backward flow occur through the incompetent valve. This is illustrated diagrammatically in Figure 18. The abnormal backward flow increases the volume of blood in which the dye is diluted during its initial traversal of the heart and, as a result, the amplitude of the dilution curve is reduced. The abnormal backflow also delays clearance of the dye during its first passage through the heart and thus causes a disproportionate prolongation of the disappearance slope.

Congenital heart disease with abnormal communications between the cardiac chambers or great vessels is associated with a right-to-left or a left-to-right shunt or both. As would be expected, these abnormal circulatory pathways produce characteristic alterations in the dilution curves recorded from such patients.[42] The characteristic curves associated with various types of congenital heart disease and the basis for their production have been described[43] and will not be considered in this presentation, except to emphasize that the abnormalities of an arterial dilution curve produced by a left-

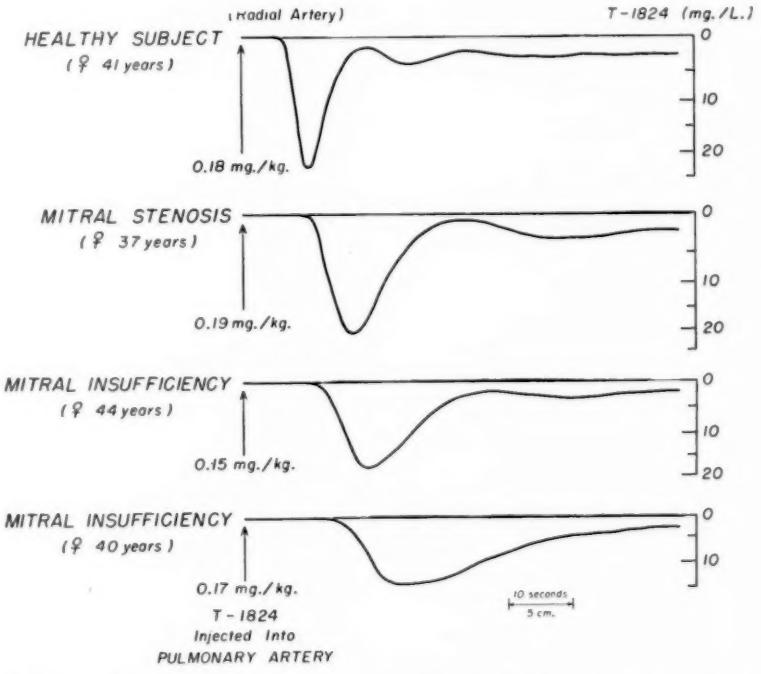

Fig. 19. Alterations in the contour of indicator-dilution curves associated with disease of the mitral valve. The curve recorded from the patient with mitral stenosis shows prolongation of all time components. The curves from the patients with mitral regurgitation show, in addition to such prolongation, a decrease in peak deflection, a disproportionate prolongation of the disappearance slope and a diminution or absence of a systemic recirculation peak.

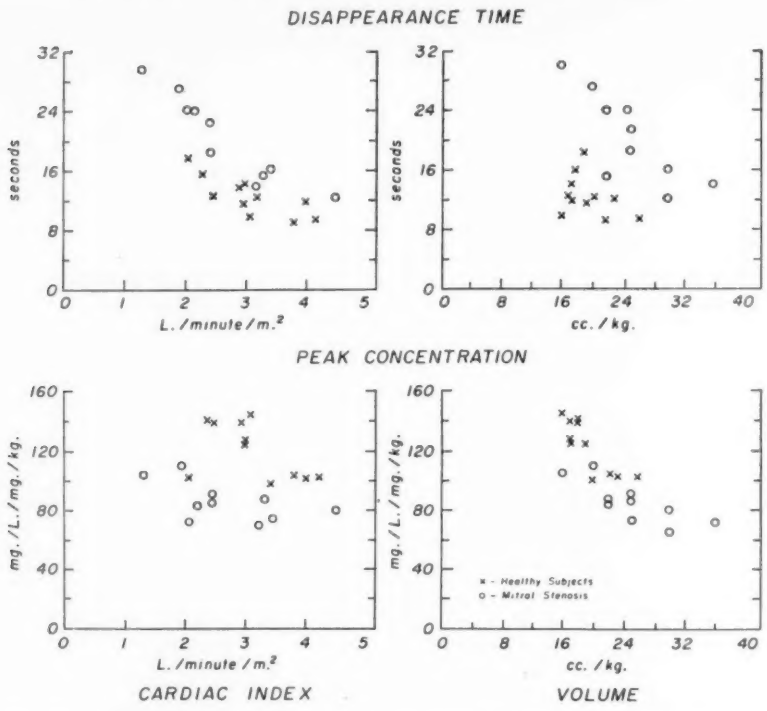

Fig. 20. Variation of a single time or concentration component of indicator-dilution curves with variation in cardiac index and central blood volume in 11 healthy persons and 10 patients with mitral stenosis. Note that these two components of disappearance time and peak concentration, both of which can be correlated with the degree of mitral regurgigation (Fig. 21), are affected in a systematic manner by variations in cardiac output or central blood volume. Therefore, if the best possible discrimination between stenosis and regurgitation is to be attained from these parameters, it is necessary to devise a means of correcting the values obtained for the variations in blood flow and central blood volume encountered in the individual patient.

to-right shunt are closely similar to those associated with severe valvular regurgitation.

DILUTION CURVES ASSOCIATED WITH VALVULAR REGURGITATION

The striking differences between the contours of indicator-dilution curves recorded from healthy persons and those from patients with severe disease of the mitral valve are illustrated in Figure 19. In contrast to the normal, the curve from the patient with congestive heart disease as a result of mitral stenosis shows proportionate prolongation of all time components. In severe mitral regurgitation, in addition to the generalized prolongation of the time components there are (1) a decrease in peak concentration of the curve, (2) a pronounced disproportionate prolongation of the disappearance slope, and (3) an absence of a systemic recirculation peak.

When a comparison is made of the dilution curves in severe mitral stenosis and in mitral regurgitation, the differences associated with these two types of valvular disease are evident. However, the differences in borderline cases are not readily discernible by simple inspection. Therefore, methods for objective quantitation of the changes produced by valvular regurgitation are desirable. The aim of the studies to be described was to develop suitable quantitative methods to measure the changes produced by mitral regurgitation.

Individual components of dilution curves affected by valvular regurgitation also are affected to a relatively great degree by the variations in cardiac output and blood volume that

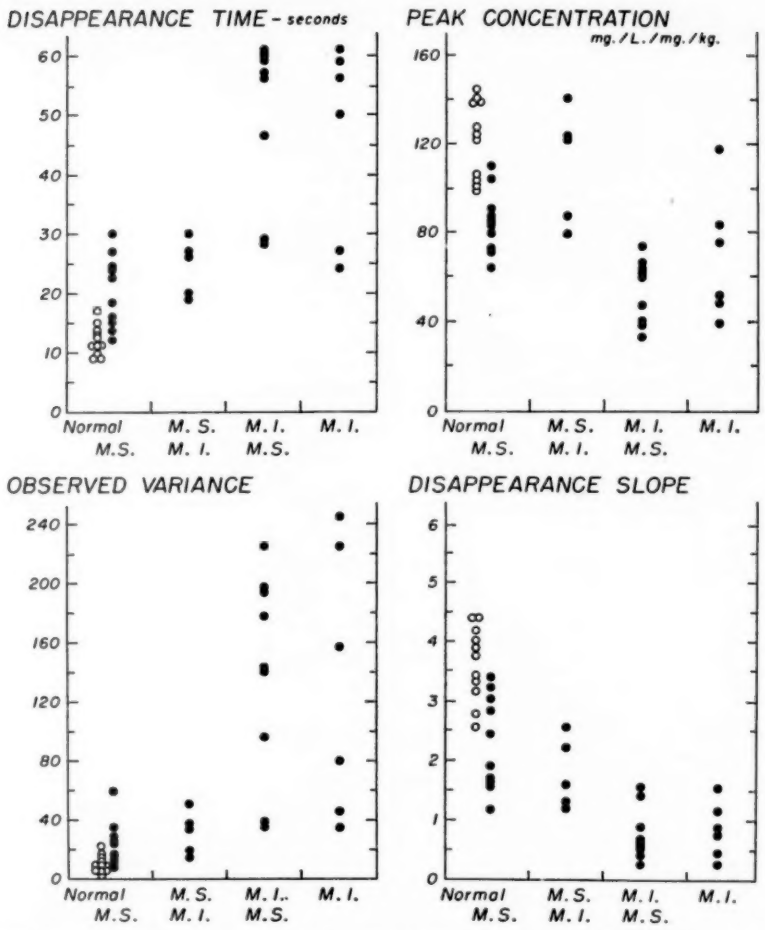

Fig. 21. Relationships of various parameters of indicator-dilution curves to the degree of mitral regurgitation. The type of mitral valvular disease is plotted on the abscissa, progressing from healthy persons (open circles) through patients with various types of mitral valvular disease (solid circles) graded as already indicated. Note that significant correlation exists between each of these parameters and the degree of regurgitation but that considerable overlapping of values occurs between patients with different categories of mitral disease. Attempts at correction of these parameters for the nonspecific effects of variations in blood flow and volume result in some improvement in the degree of discrimination obtained.

commonly occur from patient to patient. Therefore, to attain the maximal possible discriminatory effectiveness from dilution curves, it was necessary to devise methods to correct for the nonspecific effects of cardiac output and blood volume, as has been recognized previously by Broadbent and Wood[44] and by Korner and Shillingford.[45]

METHODS

To study the changes produced by valvular incompetence, dilution curves recorded at the radial artery after injection of 7.5 to 15 mg of T-1824 (Evans blue) into the pulmonary artery in 11 healthy volunteers and 30 patients with disease of the mitral valve were examined. These curves were recorded by means of a continuously recording cuvette oximeter in the manner previously described.[42,46] All persons were breathing 100 per cent oxygen. All patients underwent catheterization of the right side of the heart as previously described.[26,47]

The recorded curves then were replotted semilogarithmically after the manner described by Kinsman and associates[48] to eliminate the effect of indicator that had traversed the circulation once and was passing the sampling site a second time. Various time and concentration components as described by Wood and Swan[49] were

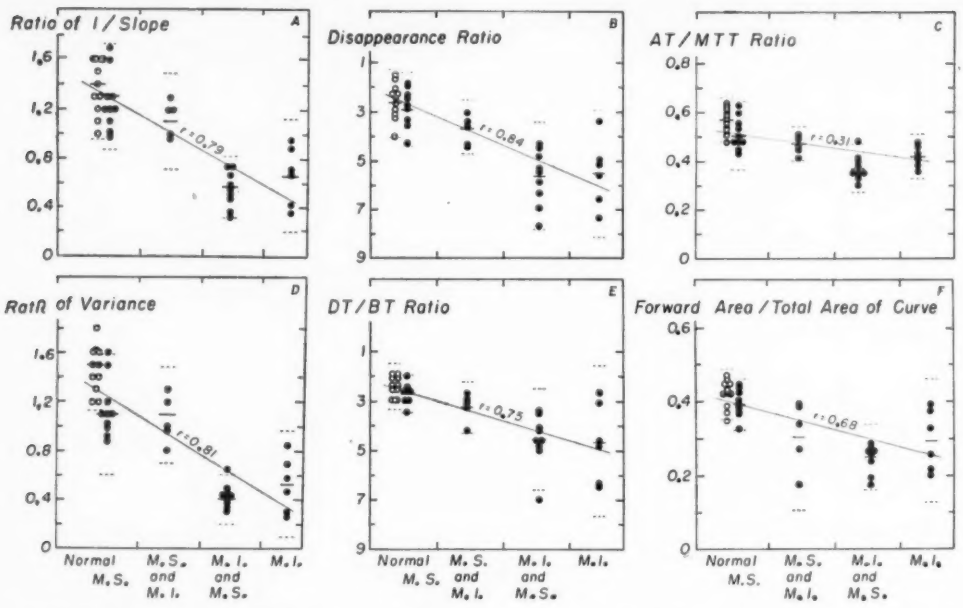

Fig. 22. Relationship of the degree of mitral regurgitation to various ratios of components of indicator-dilution curves. The long solid line in each panel is the calculated regression line with its correlation coefficient (r). The short solid horizontal lines show the mean values for each group, while the small broken lines denote twice the standard deviation for each group. Although each of the parameters shows a correlation with the degree of regurgitation, none provides complete separation of the values obtained from patients with predominant mitral stenosis and those obtained from patients with predominant mitral regurgitation. (MTT = mean transit time.)

measured. Cardiac output and central blood volume were calculated by the methods described by Stewart[50] and by Hamilton and associates.[51] The value for cardiac output was corrected for surface area and expressed as the cardiac index. The disappearance ratio described by Fox and Wood[52] was calculated. By use of the forward triangle method described by Ramirez and associates,[53] the forward area of the curve was calculated and related to the total area of the curve.[54] The reciprocal of the slope and the variance of the curves were calculated as suggested by Korner and Shillingford.[45,55] The expected values for the reciprocal of the slope and the variance were obtained by use of regression equations containing constants previously calculated from analysis of 68 dilution curves recorded at the radial artery in 13 healthy volunteers and at the radial artery or left atrium in six patients with mitral stenosis without valvular regurgitation;* these curves were recorded after injections at various sites on the right side of the heart in the normal persons and at various sites on both sides of the heart in patients with mitral disease. The constants so obtained were employed in regression equations to relate the reciprocal of the slope (or variance), the cardiac output, and the central blood volume in the correct proportions. The ratio of the expected value to the observed value was calculated to obtain the ratio of reciprocal of the slope and ratio of variance.[45,55]

These various measurements then were related to the degree of valvular regurgitation to investigate which data gave the best discrimination between patients with predominant mitral stenosis and those with predominant regurgitation. The diagnosis in all patients with pure or predominant mitral stenosis was based on the findings at operation. In the patients with pure or predominant mitral regurgitation who did not undergo surgical treatment, the diagnosis was considered to be established with certainty on the basis of clinical findings and combined catheterization of the left and right sides of the heart and the aorta.

RESULTS

The effect of variation in cardiac output and calculated central blood volume on the time and concentration components of dilution curves recorded in persons without valvular incompetence is demonstrated in Figure 20. There is an inverse relationship between the time components of the curve, such as the disappearance time, and the blood flow. There is also an inverse relationship between the central blood volume and the concentration components of the curve, such as the

* The authors are indebted to Dr. P. I. Korner for his active participation in the calculation of these constants during a visit to Rochester, Minnesota, in April, 1956.

peak concentration. As would be expected from these findings, the use of single time or concentration components of a dilution curve in relationship to the degree of valvular regurgitation gave relatively poor differentiation between the patients with predominant stenosis and those with predominant regurgitation (Fig. 21).

The use of ratios of time components, such as the ratio of the disappearance time to the build-up time (DT/BT), to minimize the effects of cardiac output on a time component such as the disappearance time has been described.[44] Since the nonspecific effects of variations in blood flow, blood volume and other factors can be partially compensated for in this manner, the DT/BT ratio gives a better separation of patients with predominant mitral stenosis from those with predominant regurgitation than does the disappearance time alone.

Korner and Shillingford,[45,55] in their attempts to quantitate valvular insufficiency from dilution curves, also recognized the necessity of correcting for the effect of cardiac output and blood volume. They attempted to eliminate these effects by comparing the measured disappearance slope of the curve and the degree of dispersion or variance of the curve with the expected values calculated from equations relating these parameters to the cardiac output and blood volume. Their results showed improvement over previous methods in discriminating between valvular regurgitation and stenosis and are surprisingly good when it is considered that the dilution curves were recorded by ear oximetry only, since dilution curves thus obtained may not accurately reflect the actual dilution curve in arterial blood.[43]

Figure 22 illustrates the results obtained in the present study by use of the methods of Korner and Shillingford and four other ratios found to be of value in differentiating predominant stenosis from predominant regurgitation. Each of these methods shows significant correlation with the degree of regurgitation. However, the overlap between the groups limits their value in this differentiation.

Disappearance Ratio and Peak Concentration: Because of these limitations, attempts were made to sharpen the discriminatory power of these individual ratios. It is logical to assume that a better differentiation of patients with stenosis from those with predominant regurgitation would result if two or more of the variables that are determined by different parameters of the dilution curve were utilized simultaneously. Figure 23 illustrates the separation obtained by using a ratio derived from two parameters shown before to have fairly good discriminatory power by themselves, namely the *disappearance ratio* and the *peak concentration.* The simultaneous use of these two parameters eliminates the overlapping between patients with predominant stenosis and those with predominant regurgitation. This method employs parameters that can be measured directly from the recorded curve and hence has important practical advantages over the more laborious methods of Korner and Shillingford.

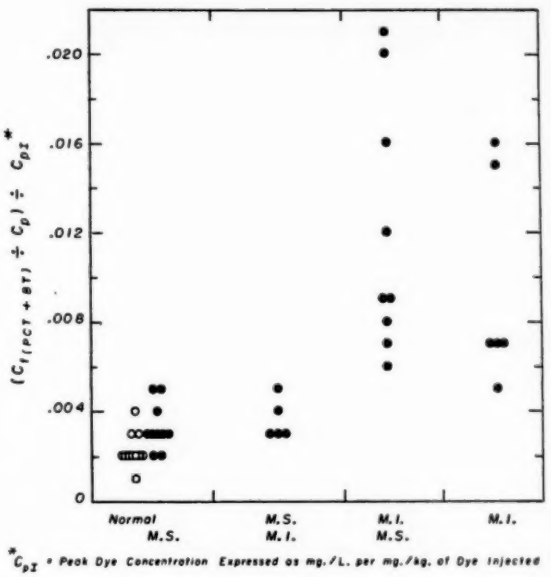

Fig. 23. Use of more than one parameter from indicator-dilution curves in the separation of patients with mitral stenosis from those with mitral regurgitation. Plotted on the ordinate is the disappearance ratio (C_t[PCT+BT] ÷ C_p) divided by the peak concentration (C_{PI}), while on the abscissa is indicated the type of mitral valvular disease. The disappearance ratio is calculated by dividing C_t-(PCT + BT), which is the concentration measured on the disappearance slope at an instant in time found by adding the build-up time of the curve to the instant of peak concentration, by C_p (the peak concentration). Note that no overlap occurs between patients with predominant stenosis and those with predominant regurgitation.

Least Concentration and Systemic Recirculation Concentration: Out of these various manipulations an even simpler method has been devised recently.[56] This method requires only the measurement of the *least concentration* and of the *systemic recirculation concentration,* the ratio of the former to the latter being used. This simple ratio gave complete separation of patients with predominant stenosis from those with predominant regurgitation in the series studied.[56] The peak concentration (C_P), the point of least concentration (C_L) between the peak deflection of the curve and the systemic recirculation peak, and the systemic recirculation concentration (C_R) were measured for curves recorded by both ear and cuvette oximeters. These terms have been defined previously.[49] The points on the curve selected for measurement of C_L and C_R are illustrated in Figure 24. The values obtained were expressed in terms of centimeters of deflection for the curves recorded by the ear oximeter and the curves recorded by cuvette oximeter at the radial artery. These values were converted to milligrams of T-1824 per liter of blood for the curves recorded by the cuvette oximeter. The ratio of these measurements for each of the curves

was calculated, that is, least concentration (C_L) divided by systemic recirculation concentration (C_R).

For the curves in which a systemic recirculation peak was not discernible, attempts were made to utilize other numerical values in place of C_L and C_R in the following manner: The relationship between the build-up time, the least concentration time and the systemic recirculation time was examined in a series of dilution curves recorded at the radial artery after injections of dye into the pulmonary artery of 20 patients with mitral valvular disease. It was noted in these patients that the average

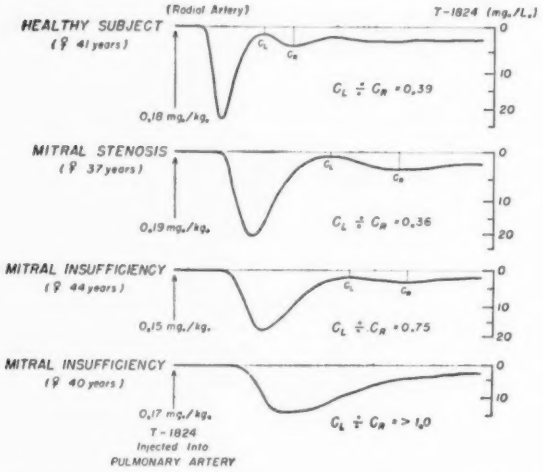

Fig. 24. Changes in contour and the points of least concentration (C_L) and systemic recirculation concentration (C_R) of dilution curves from a healthy person and three patients with mitral valvular disease. Values calculated for the ratio C_L/C_R for each curve are shown. In the curve with no detectable systemic recirculation recorded from a patient with severe mitral regurgitation, the value for the ratio C_L/C_R is designated as greater than 1.

time from the first detectable appearance of the dye to the occurrence of the least concentration was 2.3 times the build-up time (BT) of the curve. Similarly, the average time from first appearance of the dye to the systemic recirculation peak was 3.8 times the build-up time.

This information concerning the average instances of occurrence of the point of least concentration and the systemic recirculation peak of a dilution curve in relation to the build-up time of the curve then was used as a basis for obtaining concentration values designated $C_{AT+2.3BT}$ and $C_{AT+3.8BT}$ which could be to a degree analogous to C_L and C_R, respectively. The ratio $(C_{AT+2.3BT}) \div (C_{+AT3.8BT})$ was calculated and assumed to be analogous to the C_L/C_R ratio for the dilution curves on which no systemic recirculation peak could be detected.

Absent Recirculation Peak in Mitral Regurgitation: Well-marked systemic recirculation peaks were evident on the dilution curves recorded at the radial artery in each of the normal persons and in each of the patients with either pure mitral stenosis or predominant stenosis with some degree of mitral regurgitation. However, no detectable systemic recirculation peak was obtained in four of the nine patients with predominant mitral regurgitation and in three of the six patients with pure mitral regurgitation.[56] This difference in the dilution curves along with others associated with mitral regurgitation is illustrated in Figure 24, which shows curves recorded from a healthy person and three patients with disease of the mitral valve. The points of measurement of the deflections C_L and C_R are indicated on these curves, and the ratios of C_L/C_R calculated from these values are given. The bottom dilution curve, recorded from a patient with severe mitral regurgitation, had no detectable recirculation peak; in this case, the value for C_L/C_R was designated as greater than 1.

Correlation of C_L/C_R Ratio and Degree of Regurgitation: The deflections at least concentration C_L and recirculation concentration C_R measured in centimeters were converted to milligrams per liter of blood per milligram of dye injected per kilogram of body weight. A positive correlation was obtained when the least concentration expressed in these units was plotted against the degree of regurgitation. There was, however, considerable overlapping of values obtained for patients with mild and severe degrees of regurgitation, so that complete separation of patients with predominant stenosis from those with predominant regurgitation was not attained. When the systemic recirculation peak concentration expressed in these units was plotted against the degree of regurgitation, a tendency toward a negative correlation could be discerned (Fig. 25). Despite the rather poor correlation of these parameters when taken singly, a striking correlation was obtained between their ratio (C_L/C_R) and the degree of regurgitation (Fig. 26). Complete separation of values for patients with predominant stenosis from values for patients with predominant regurgitation was obtained from the curves recorded by cuvette oximeter in this series of patients. However, analysis of an additional series of 30 patients with mitral valvular disease investigated subsequent to this comparative study of the different methods for distinguishing stenosis and regurgitation has shown a number of instances of overlap between the values for C_L/C_R ratios in the two categories of patients with both significant stenosis and regurgitation of the mitral valve. The overlap of values into the range of predominant regurgitation ($C_L/C_R > 0.65$, Figure 26) was particularly prominent in the patients categorized as having predominant mitral stenosis with significant mitral regurgitation. In four of the 12 patients classified in this group in this additional series of patients, the C_L/C_R ratio was greater than 0.65. The C_L/C_R ratios calculated on the basis of centimeters of deflection or after conversion to milligrams per liter were closely similar, so that, for practical purposes, simple measurements expressed as centimeters of deflection and made directly from the recorded curve are satisfactory for calculation of this ratio. Presumably because

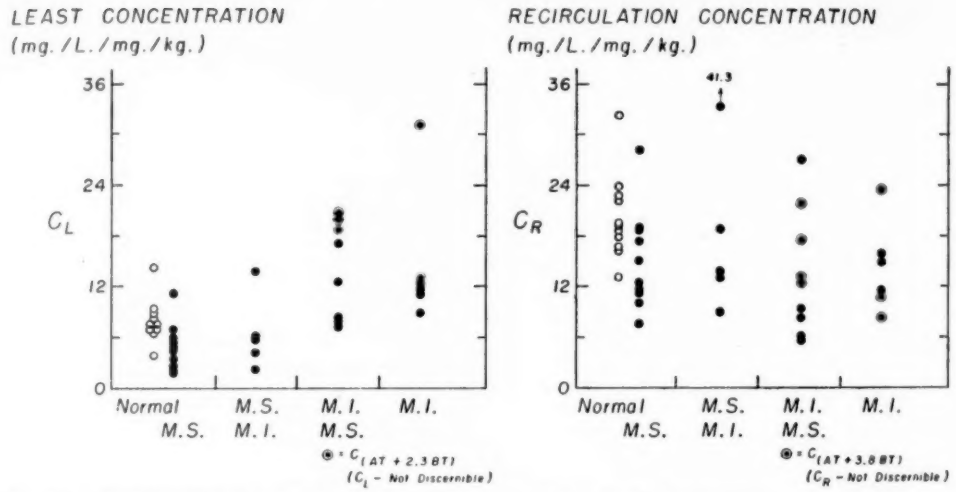

Fig. 25. Relationship of the degree of mitral regurgitation to the least concentration (C_L) and the systemic recirculation concentration (C_R), expressed as milligrams per liter of blood per nilligram of dye injected per kilogram of body weight. Note the tendency for a positive correlation of C_L and a negative correlation of C_R with the degree of mitral regurgitation and the extensive overlapping of the values obtained for the various groups.

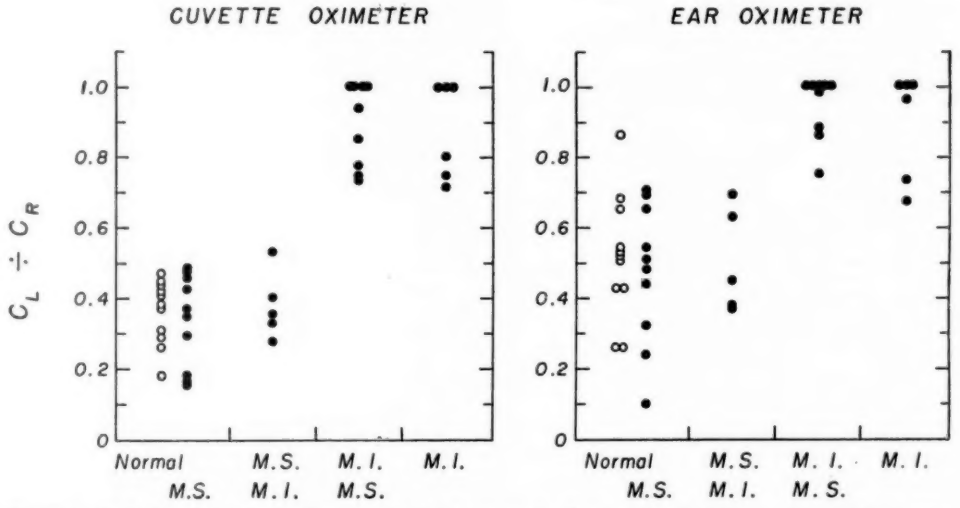

Fig. 26. Relationship of the degree of mitral regurgitation to the ratio between the least concentration and the systemic recirculation concentration. The ratios were calculated directly from the deflections measured from the recorded dye curves without conversion to concentration of dye in the blood. Ratios determined from ear-oximeter curves are on the right and those from cuvette-oximeter curves recorded at the radial artery are on the left. The data were collected from the same series of patients and healthy persons as were the data in Figures 21, 22, 23, and 25. Note the complete separation of patients with predominant mitral stenosis from those with predominant mitral regurgitation by means of the values obtained from cuvette-oximeter curves. The separation of these patients by means of ear-oximeter curves is not complete, probably because of the poor definition (slurring) that often characterizes dilution curves recorded at the ear.

of the slurring frequently evident in dilution curves recorded at the ear,[42] the values for C_L/C_R ratios calculated from ear-oximeter curves from patients with predominant stenosis overlapped those from patients with predominant regurgitation (Fig. 26).

Dilution curves without a detectable recirculation peak were obtained only in patients with severe mitral regurgitation. For practical diagnostic purposes, it was found to be sufficient to express the C_L/C_R ratios for such curves as greater than 1. Therefore, calculation of

$(C_{AT+\,2.3BT})/(C_{AT+\,2.8BT})$ ratios for these curves offers no apparent advantage.

As is true for other methods of analysis of dilution curves, the C_L/C_R ratio does not differentiate between the abnormalities produced in dilution curves by valvular regurgitation and those produced by a left-to-right shunt.[44] Additional data that frequently make possible localization of regurgitation to a particular heart valve or of the site of a left-to-right shunt can be obtained by comparison of the C_L/C_R ratios from multiple curves from the same patient obtained by use of different injection sites or sampling sites or both.[87] However, in the interpretation of differences in C_L/C_R ratios from curves recorded in this manner, it is necessary to keep in mind that, in the normal circulation, the C_L/C_R ratio increases as the injection or sampling site is shifted to more peripheral locations in the venous or arterial circulation, respectively.[88]

Summary of the Differentiation of Mitral Stenosis and Regurgitation by Means of Dilution Curves Recorded from the Systemic Arterial Circulation After Injection of Dye Into the Venous Circulation: Indicator-dilution curves recorded by oximetry at the radial artery after injection of T-1824 into the pulmonary artery in 11 healthy volunteers and 30 patients with disease of the mitral valve were examined in an effort to find, if possible, a method for discriminating between predominant mitral stenosis and predominant mitral regurgitation. The alterations in contour resulting from nonspecific changes in cardiac output and central blood volume that commonly occur from patient to patient were compensated for by calculating various ratios of individual time or concentration components and by using the disappearance slope and variance ratios described by Korner and Shillingford. A correlation was demonstrated between each of the ratios studied and the degree of regurgitation, but overlapping of values prevented complete separation of patients with predominant mitral stenosis from those with predominant mitral regurgitation. Combination of two parameters of dilution curves was found to increase the discriminatory power of these ratios by reducing or eliminating the overlap between values for patients with predominant stenosis and values for those with regurgitation.

The use of values based on parameters that can be measured directly from the recorded curve has practical advantages over the more laborious methods of Korner and Shillingford in the differentiation of patients with valvular stenosis from those with regurgitation.

The data suggest that the values for the volume of regurgitant flow in individual patients calculated by the methods of Korner and Shillingford are subject to large error.

In the series of 30 patients with mitral valvular disease, the values for C_L/C_R ratios calculated from dilution curves recorded at the radial artery in patients with predominant mitral stenosis did not overlap those calculated for patients with predominant mitral regurgitation. Some degree of overlap was obtained in the ratios calculated from curves recorded by the ear oximeter. However, study of C_L/C_R ratios in an additional series of patients revealed four of 12 patients classified as having predominant mitral stenosis with significant regurgitation whose C_L/C_R ratios were more than 0.65, which was the lower range of the values obtained in patients with predominant mitral regurgitation. In spite of this overlap of values in patients with combined lesions of the mitral valve, this simple ratio is considered to be a valuable adjunct in the differential diagnosis of mitral valvular disease and has the additional practical advantage of ready applicability, since only two values are required, both of which can be measured directly from recorded dilution curves without the necessity of time-consuming mathematical manipulations.

Although the study of dilution curves recorded from the arterial circulation has considerably increased the accuracy of diagnosis in problem cases of mitral valvular disease in a large series of patients studied in this laboratory, these methods have failed to provide a completely uniform discrimination between patients with predominant mitral stenosis and predominant mitral regurgitation. Also, attempts to obtain reasonably accurate estimates of the volume of regurgitant flow have been disappointing.

Demonstration of Mitral Regurgitation by Means of Dilution Curves Recorded from the Left Atrium

The development of methods[26,59–63] for the simultaneous recording of dilution curves from the left atrium and systemic arterial and venous

circulation following injections of indicator into the left ventricle, left atrium, aorta, and various sites in the venous circulation considerably extends the scope of possible methods of attacking this problem.

After injection of an indicator into the left ventricle in the presence of an incompetent mitral valve, movement of the resulting mixture of blood and dye may be in two directions, namely backward into the left atrium and forward into the aorta. If an indicator-dilution curve is recorded from the left atrium after injection of dye into the left ventricle, the early appearance of dye in the atrium indicates that dye has regurgitated through the mitral valve from the left ventricle (Fig. 27*a*). The failure to detect early appearing dye suggests that regurgitation has not occurred and thus that the mitral valve is competent (Fig. 27*b*).[59,61] Comparison of the area of the rapidly appearing portion of such a left atrial dilution curve with the areas of curves recorded from the left atrium after injection of indicator directly into the left atrium or into the pulmonary artery should provide an estimate of the quantity of blood regurgitated through the mitral valve if complete mixing of dye and blood in the left atrium has occurred under both of these circumstances.[60] The following is a description of this method and the results obtained in its application in animals and during catheterization of the left side of the heart in patients with disease of the mitral valve.

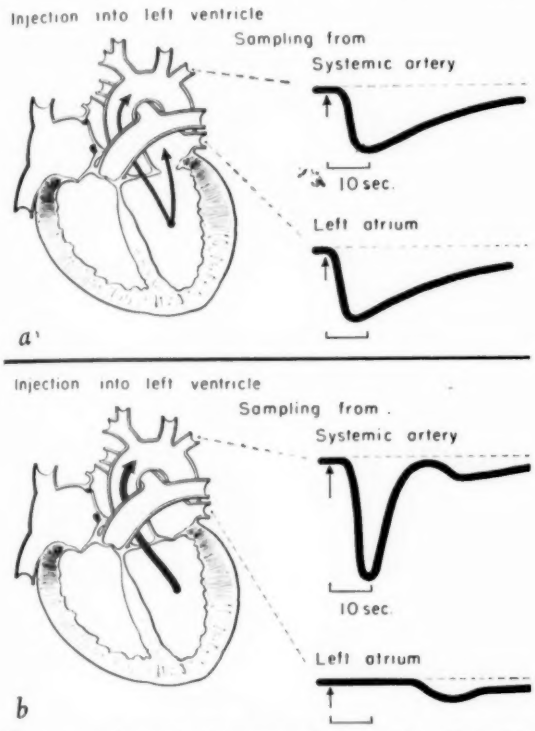

Fig. 27. Schematic diagram of the paths taken by indicator injected into the left ventricle in the presence (*a*) and in the absence (*b*) of mitral regurgitation. Dilution curves recorded at the left atrium and a systemic (radial) artery are shown. When the valve is competent, no dye appears in the left atrium before it appears in the systemic arterial system. When mitral regurgitation is present, dye injected into the left ventricle is regurgitated immediately through the mitral valve and thus is detected in the left atrium prior to its arrival at the systemic artery. In addition to early appearing dye in the left atrium, the contours of the dilution curve recorded at the systemic artery show, in comparison with the normal, the abnormalities characteristic of valvular regurgitation, namely reduced deflection, disproportionate prolongation of the disappearance phase, and the absence of a systemic recirculation peak.

MATERIALS AND METHODS

Fifteen adult mongrel dogs were used in this study. All were anesthetized with amobarbital (amytal) sodium and ether, and a cuffed endotracheal tube was used for maintenance of respiration by a mechanical respirator. Ten animals were normal dogs weighing 16 to 27 kg, with a mean of 19 kg. Acute mitral regurgitation was surgically created in seven of these 10 normal dogs in the manner described by Kuykendall and associates.[64] Mitral regurgitation had been surgically created approximately six to eight weeks prior to this study in five additional dogs weighing 16 to 20 kg, with a mean of 18 kg, which were classified as having chronic mitral regurgitation.* Plastic catheters were introduced via needle puncture directly into the left ventricle, left atrium, pulmonary artery, and femoral artery. Cuvette oximeters were connected to the catheters in the left atrium and femoral artery for the continuous recording of dilution curves in a manner previously described.[42] The areas encompassed by the dilution curves recorded at the left atrium after injection of T-1824 (5 to 10 mg) into the left ventricle, left atrium, and pulmonary artery were obtained by the "triangle method" described by Warner and Wood.[65] The formulae used for calculation of these areas were

$$A_1 = (PT \cdot C_P/2)\, L_V$$

and

$$A_2 = (PT \cdot C_P/2)\, L_A$$

* The authors are indebted to Drs. S. J. Kuykendall, F. H. Ellis, Jr., and J. H. Grindlay for making possible these studies during their investigations of a surgical method for creation and repair of mitral regurgitation.[64]

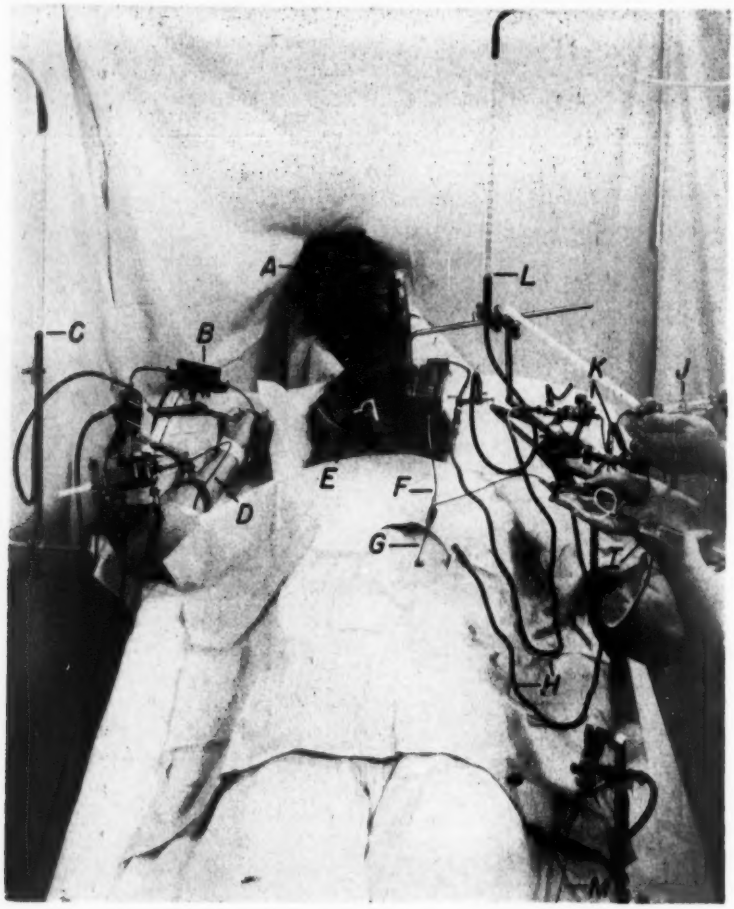

Fig. 28. Apparatus for simultaneous recording of indicator-dilution curves at the left atrium and left radial artery after injection of indicator into the left ventricle, left atrium and various sites in the right side of the heart or the aorta during combined catheterization of the right and left sides of the heart and the aorta. (A) Twin-beam oscilloscope for continuous display of patient's electrocardiogram and the pressure (left atrial or left ventricular) being transmitted through the catheter in the left side of the heart. (B) Cuvette oximeter attached to a needle in the left radial artery and to a strain gauge and burette blood-sampling system (C) via a three-way stopcock assembly that allows interchangeable recording of arterial pressure or withdrawal of arterial blood through the cuvette. (D) Catheter to right side of heart introduced by percutaneous needle puncture, with its tip manipulated into the pulmonary artery, for recording of pressure by the strain gauge, injection of dye at selected sites on the right side of the heart, withdrawal of blood for gas analysis or recording of dilution curves from the right side of the heart[63] after injection of indicator via the catheter in the left side of the heart or the aorta. (E) Ear oximeter for continuous monitoring of arterial oxygen saturation and for recording of dilution curves. (F) Cuvette oximeter attached to the side arm of a special 18T-gauge needle assembly (G), the tip of which is in the left atrium. The cuvette oximeter is attached to a three-way stopcock assembly that makes possible interchangeable recording of left atrial pressure via a malleable lead tube (H) connected to a strain-gauge (Statham P23-D) manometer (K) and of dilution curves in left atrial blood withdrawn by suction into a burette (L) via the residual lumen between the catheter in the left side of the heart and the needle shaft. The indicator dye, contained in a specially designed calibrated syringe (J), is injected via the catheter in the left side of the heart. Immediately after the injection, the catheter is rapidly flushed free of dye by the injection of saline solution contained in another syringe (I). During recording of dilution curves, each milliliter of blood flow into the burettes (C and L) is signalled on the record. In the interval between injections of indicator, the catheter in the left side of the heart is connected via its lead tubing (H) to another strain-gauge (Statham P23-G) manometer (K). This makes possible simultaneous recording of left ventricular, left atrial, pulmonary arterial and aortic pressures, as previously described.[26] Another strain-gauge (Statham P23-G) manometer (M) is attached to a catheter introduced into the thoracic aorta via percutaneous puncture of the right femoral artery for recording of aortic pressure or injections of dye just above or at graded distances distal to the aortic valve.[57,66,67]

in which C_P equals the peak concentration of the curve in milligrams per liter, PT the passage time (seconds), A_1 the area of the curve representing early appearing dye recorded at the left atrium after injection of dye into the left ventricle, and A_2 the area of the curve recorded at the left atrium after injection of dye into the left atrium or pulmonary artery. The ratio A_1/A_2 is related to the fraction of the blood-dye mixture regurgitated through the mitral valve if uniform mixing of the left atrial blood with dye injected or regurgitated into the left atrium can be assumed. To test this assumption, the ratio A_1/A_2 was related to the degree of regurgitation estimated by palpation at operation.

Dye-dilution curves recorded simultaneously from the left atrium and radial artery in 20 patients with disease of the mitral valve also were examined. All patients underwent catheterization of the right and left sides of the heart in a manner previously described.[26,47] In each patient classified as having pure or predominant mitral stenosis, the diagnosis was based on palpation at the time of operation. In those patients classified as having predominant or pure mitral regurgitation who did not undergo operation, the diagnosis was based on a combination of clinical findings and data obtained during combined catheterization of the right and left sides of the heart and the aorta. Dye-dilution curves were recorded simultaneously by cuvette oximeters from the left atrium and the radial artery after injections of T-1824 (7.5 to 15 mg) into the left ventricle, left atrium, and pulmonary artery. The technic used for simultaneous recording of dye curves from the left atrium and radial artery after injection of dye into the left or right side of the heart[26,59] is illustrated in Figure 28. The areas and the ratios of the areas of these dilution curves were calculated by the triangle method, as in the experimental animals already mentioned. The calculated fractions of dye regurgitated through the mitral valve estimated as the ratios of these areas were related to the degree of mitral regurgitation believed to be present on the basis of surgical, clinical, and catheterization findings.

RESULTS

An original photokymographic recording of indicator-dilution curves recorded simultaneously from the left atrium, left radial artery, and left ear, together with other physiologic variables during combined left-heart, right-heart and aortic catheterization, is shown in Figure 29. A reproduction of the radial and

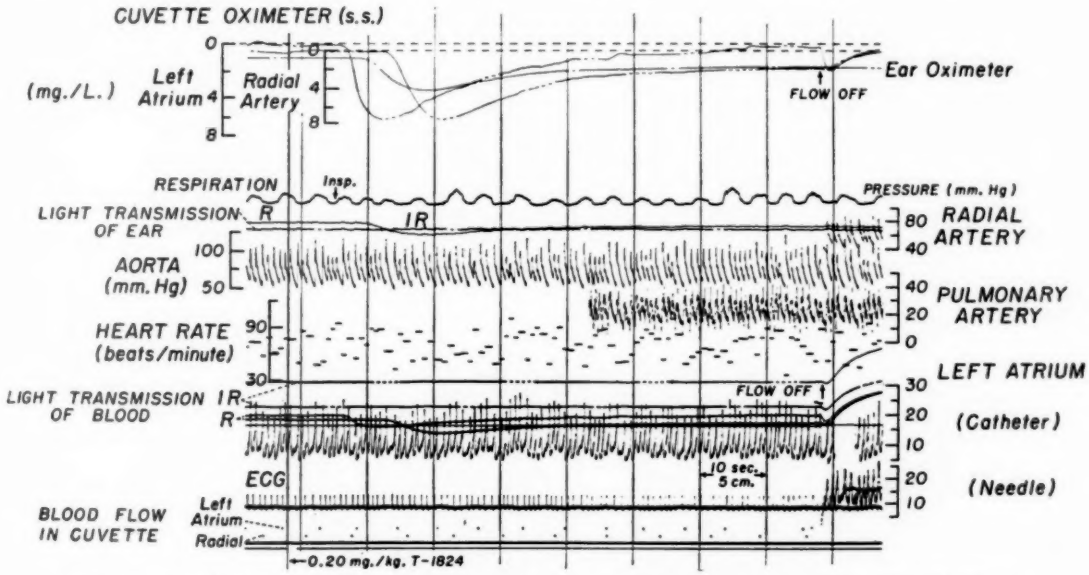

Fig. 29. Original photokymographic recording of indicator-dilution curves recorded simultaneously from the left atrium, left radial artery and left ear, with other physiologic variables, during combined left-heart, right-heart, and aortic catheterization by means of the assembly shown in Figure 28. The patient was a 29-year-old woman with mitral regurgitation and atrial fibrillation. The indicator was injected into the pulmonary artery. Note the disproportionate prolongation of the disappearance slope and absence of a systemic recirculation peak in all three dilution curves, which are characteristic of severe mitral regurgitation, and that the curve recorded by the ear oximeter is a damped version of the curves recorded directly from flowing blood by means of cuvette oximeters. The signals at the bottom of the record indicate each millimeter of blood flow through the two cuvette oximeters. The recordings of left atrial pressure show the high peaked V waves characteristic of severe mitral regurgitation. The letters R and IR indicate the recordings of the transmission of red and infrared light through the ear and left atrial and radial arterial blood, respectively.

left atrial dilution curves obtained from such recordings after injections into the left ventricle, left atrium, and pulmonary artery of a patient with severe mitral regurgitation is shown in Figure 30. These curves show the abnormal features that, in the proved absence of a left-to-right shunt, are indicative of severe valvular regurgitation. Furthermore, dye injected into the left ventricle was detected immediately and in large quantity in the left atrium. This is in contrast to the findings in mitral stenosis without regurgitation, in which the detection of dye at the left atrium is delayed for the time required for the dyed blood to be ejected from the left ventricle, traverse the systemic and pulmonary circulations, and return to the left atrium.[59] In the patient represented in Figure 30, as often is true in patients with severe mitral regurgitation, it is noteworthy that the area under the dilution curve recorded from the left atrium after injection into the left ventricle is

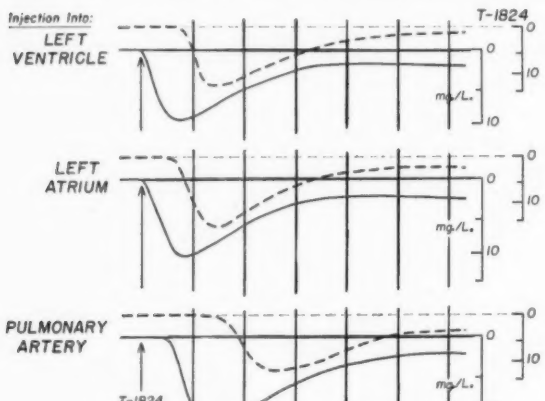

Fig. 30.

Fig. 30. Demonstration by indicator-dilution curves of valvular regurgitation of a severe degree and its localization to the mitral valve by detection of early appearing dye in the left atrium of a 40-year-old woman after its injection into the left ventricle (top panel). The instant of injection of identical doses of T-1824 is indicated by the vertical arrow, and the dilution curves are recorded simultaneously at the radial artery (broken line) and left atrium (solid line). The similarity of the areas subtended by the left atrial curves after injections into the left ventricle and directly into the left atrium suggests that the volume of blood regurgitated through the mitral valve during systole must be much larger than the volume ejected forward into the aorta.

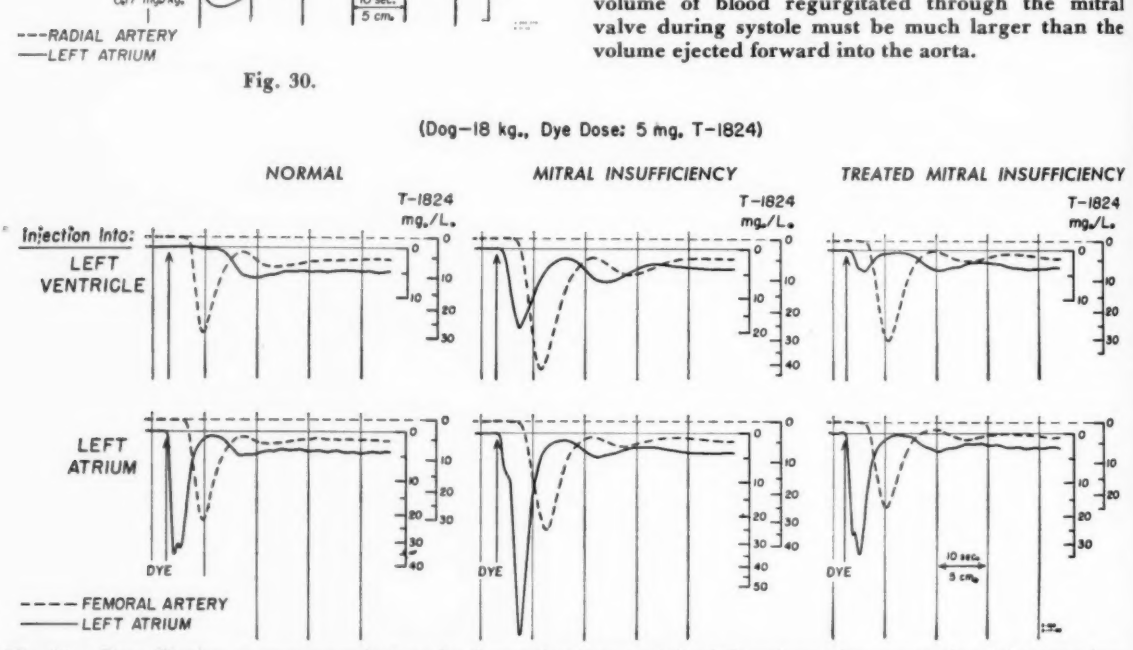

Fig. 31. Dye-dilution curves recorded at the femoral artery and the left atrium after successive injections into the left ventricle and left atrium of a dog before and after surgical production of mitral regurgitation and after attempted repair of the condition. Note the absence of early appearing dye in the left atrium after injection of dye into the left ventricle of the normal dog. A large amount of early appearing dye was detected in the left atrium after injection of dye into the left ventricle after the surgical creation of mitral regurgitation. After attempted abolition of the regurgitation, the amount of rapidly appearing dye detected in the left atrium after injection into the left ventricle is reduced, indicating that partial correction has been accomplished. Note the normal appearance of the dye curve from the femoral artery in spite of the presence of severe mitral regurgitation (center panel).

nearly equal to the area encompassed by the dilution curve recorded from the left atrium after injection directly into this chamber or into the pulmonary artery. This suggests that the left atrium and left ventricle functionally behave like a single mixing chamber and that the forward flow of dyed blood into the aorta with each systole must be much smaller than the volume flowing retrogradely into the left atrium.

An example of dilution curves recorded simultaneously from the left atrium and femoral artery before and after experimental production of mitral regurgitation in the dog and after at-

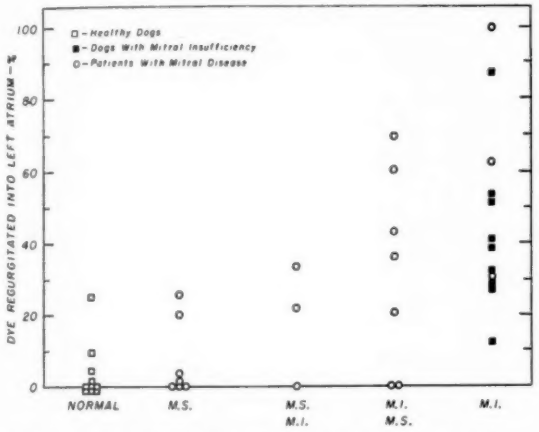

Fig. 32. Relationships of the degree of mitral regurgitation as estimated surgically to the proportion of dye regurgitated into the left atrium after injection into the left ventricle in a group of dogs and in patients with disease of the mitral valve. A positive correlation is present between the amount of dye regurgitated and the degree of mitral regurgitation. Note, however, that false positive and false negative indications of mitral regurgitation were obtained in both dogs and patients.

tempted repair of the lesion by circumferential suture is shown in Figure 31. In the normal animal (left panel), practically no dye appeared at the left atrium after its injection into the left ventricle until recirculation through the systemic and pulmonary circulations had occurred. After the production of acute mitral regurgitation, a large amount of early appearing dye was detected in the left atrium (middle panel). The attempted repair was apparently only partly successful (right panel), since a smaller but significant amount of early appearing dye was detected in the left atrium after injection of dye into the left ventricle. The dilution curves recorded at the femoral artery under these different circumstances are similar to one another and apparently are not affected greatly by the production of acute mitral regurgitation that was judged by the surgeon on the basis of direct palpation to be severe. The normality of the contour of the femoral dilution curves despite the presence of severe acute mitral regurgitation illustrates the errors that can occur in attempting to calculate the actual volume of regurgitation on the basis of dilution curves recorded at a systemic artery even by methods designed to compensate for differences in cardiac output and central blood volume.[45]

Correlation of A_1/A_2 Ratio and Degree of Regurgitation: To evaluate the efficacy of dilution curves recorded at the left atrium in the detection and quantitation of valvular regurgitation, the ratio A_1/A_2, calculated as already described, was plotted against the degree of regurgitation judged by the surgeon* to be present on the basis of palpatory findings (Fig. 32). In each instance, in an effort to reduce possible errors due to non-uniform mixing of dye and atrial blood, after injection of dye directly into the left atrium, the area of the left atrial curve recorded after injection into the pulmonary artery was used as the value for A_2 in the formula. In the two columns in the left part of Figure 32 are included data, respectively, from the 10 healthy dogs into which injections were made into the left ventricle, left atrium, and pulmonary artery, and from the seven patients found at operation to have "pure" mitral stenosis. In three of the dogs and three of the patients, early appearing dye was detected at the left atrium in moderate amount (*false positives*). Of the 10 patients with combined mitral regurgitation and stenosis, three (one with moderate and two with predominant regurgitation) failed to show early appearing dye (*false negatives*). In all of the dogs and in the three patients with "pure" regurgitation, moderate to large amounts of early appearing dye were detected in the left atrium. As would be ex-

* The authors are indebted to Drs. J. W. Kirklin and F. H. Ellis, Jr. for their estimates of the type and severity of malfunction of the mitral valve arrived at during mitral commissurotomy carried out on each of the patients.

pected, a positive correlation exists between the estimated quantity of dye regurgitated through the mitral valve and the severity of regurgitation, but a considerable overlap exists between the different groups.

COMMENT

Since uniform mixing of left atrial blood and indicator injected or regurgitated into the left atrium is an essential requirement, the failure of this method to provide a uniformly reliable means of discriminating between patients with mitral stenosis and those with mitral regurgitation, although disappointing, was not unexpected.

Non-uniform Atrial and Ventricular Mixing: Indicator-dilution studies carried out both in dogs and in patients with atrial septal defect alone or in combination with complete anomalous pulmonary venous connection have demonstrated that uniform mixing does not occur in either the right or left atrium.[68–71] Dye-dilution curves recorded after injections of indicator at different sites in the right [72] or left ventricle[73] in patients with ventricular septal defects have demonstrated that uniform mixing does not occur in either of the ventricles. The uniform finding in a series of patients with anatomically common ventricle (diagnosis confirmed at necropsy) of striking differences between the oxygen content of blood from the pulmonary artery and that from the aorta and between dilution curves recorded after injection into the left and into the right atrium demonstrates pronounced preferential flow of left atrial blood into the aorta. Such a preferential flow from the respective atria to the pulmonary artery and aorta also provides conclusive proof that uniform mixing frequently does not occur in an actively functioning ventricular chamber.[74]

An extreme example of non-uniform mixing of dye and blood in the left atrium in a patient with mitral stenosis is shown in Figure 33. In this instance, even when dye was injected *directly* into the left atrium, dye was not detected at the sampling site in this chamber until after recirculation through the systemic and pulmonary circulation had occurred. A normal-appearing curve was obtained from the same left atrial sampling site after injection of dye into the superior vena cava. This degree of non-uniform mixing in the left atrium has been encountered only infrequently in the series of 50 patients in whom dye curves have been recorded simultaneously at the left atrium and radial artery after injections of indicator into the left atrium and pulmonary artery. Lesser degrees of nonmixing, as evidenced by a smaller deflection of the left atrial curve following left atrial injection than following injection into the pulmonary artery, were found in 45 per cent of the patients studied. Evidence of severe

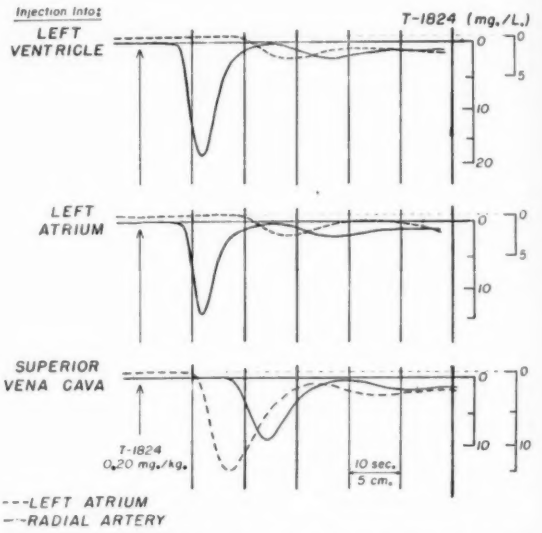

Fig. 33. Nonmixing of dye injected into the left atrium in a patient with "pure" mitral stenosis (diagnosis confirmed at operation). No early appearing dye was detected at the left atrial sampling site after injection into the left ventricle, suggesting that mitral regurgitation was not present. However, note that no early appearing dye was detected at this site even when the indicator was injected directly into the left atrium, indicating a severe degree of non-uniform mixing in this chamber. An essentially normal curve was recorded at this same left atrial sampling site after injection into the superior vena cava.

degrees of nonmixing usually is not encountered in patients with severe regurgitation, probably owing to the mixing action of the regurgitant stream in the left atrium. While false negative results (failure to detect rapidly appearing dye in the left atrium after injection into the left ventricle in the presence of mitral regurgitation) may be caused by nonmixing of

indicator in the left atrium, the same result may be, and perhaps is, more frequently due to non-uniform mixing in the left ventricle; this may result in absence of dye from the portion of the ventricular blood that is regurgitated, as might occur with an injection of dye into the outflow tract of the left ventricle, from which most of the dyed blood would be ejected preferentially into the aorta.

Backflow in Absence of Regurgitation: False positive results (detection of early appearing dye in the left atrium after injection into the left ventricle in the absence of mitral regurgitation) could be caused by temporary displacement of the tip of the left ventricular catheter through the mitral valve into the left atrium during the injection, or to the occurrence of backflow through the normally functioning mitral valve. Approximately one-third of the normal dogs in the present study showed small amounts of early appearing dye in the left atrium after left ventricular injection. However, determinations in the same animals carried out before, during, and after electrically induced atrial fibrillation failed to confirm the report of Daley and coworkers[75] that atrial fibrillation increased mitral regurgitation in normal dogs. Indirect evidence has been cited suggesting the occurrence of backflow through apparently competent atrioventricular valves,[36] and angiographic studies after injection into the ventricle also have provided evidence that such backflow may occur.[76]

It is not considered probable that the presence of the small catheter (outside diameter of 0.8 mm) in the valve could produce significant regurgitation. This possibility can be disregarded in the animal experiments, since the ventricular catheter was introduced directly by needle puncture of the muscle wall instead of through the valve, as was done in the studies on patients.

The methods for calculation of regurgitant flow through the mitral valve and other parameters recently described by Conn and coworkers[77] have not been applied to these data. However, nonuniform mixing of indicator and blood and other factors already discussed likewise constitute a serious deterrent to the successful application of these methods.

SUMMARY OF DILUTION CURVE DATA

Dilution curves recorded from the left atrium after injection of indicator into the left ventricle of dogs and of patients with disease of the mitral valve were investigated as a means of detecting and estimating the severity of mitral regurgitation. False negative and false positive indications of mitral regurgitation were encountered with disappointing frequency. Non-uniform mixing of the dye injected into the ventricle and of that injected or regurgitated into the left atrium was demonstrated to be the most likely cause of the discrepancies observed. None of the indicator-dilution methods described above have provided completely uniform differentiation of patients with predominant stenosis and those with predominant regurgitation. However, in the absence of a left-to-right shunt, certain abnormalities of the dilution curve, such as absence of a systemic recirculation peak or the presence of severe disproportionate prolongation of the disappearance slope, never have been found in patients without severe valvular regurgitation. When the valvular regurgitation is such as to produce distinct abnormalities of dilution curves, variations of the indicator-dilution technic can be used to determine at which of the four heart valves the regurgitation is occurring.

Localization of Valvular Regurgitation

Localization of an arteriovenous shunt or valvular regurgitative defects can be accomplished during catheterization of the right or left side of the heart or the aorta by studying the similarity or dissimilarity in contour of dilution curves obtained by use of (1) multiple, appropriately selected injection sites, (2) multiple, appropriately selected sampling sites, or (3) combinations of these two technics.

Localization of an incompetent valve from dilution curves recorded at a single peripheral sampling site after injections at multiple selected sites requires (a) a normal contour at the periphery after injection just distal to the next competent valve downstream to the incompetent valve and (b) an abnormal curve after injection at an upstream site or immediately distal to an incompetent valve.

Localization of an incompetent valve by use of multiple sampling sites is possible with a single injection of indicator into the venous circulation, since (a) an essentially normal curve may be recorded from sites in the right or left side of the heart upstream to a competent valve and (b) simultaneously, an abnormal curve will be recorded from sites at or downstream to the incompetent valve.

Demonstration of Aortic Regurgitation: The simplest application of these principles is the demonstration of competence or incompetence of the aortic valve.[66] In Figure 34, the curve recorded after injection of dye via a catheter placed just distal to a normally functioning aortic valve is characterized by a normal contour; the curve recorded after injection distal to an incompetent aortic valve is grossly abnormal and, in the absence of a left-to-right shunt from the aorta, is diagnostic of aortic regurgitation. In severe regurgitation, the peak deflection is relatively small, the disappearance slope is prolonged as a result of slow clearing of regurgitated dye from the left ventricle, and a systemic recirculation peak is not visible.

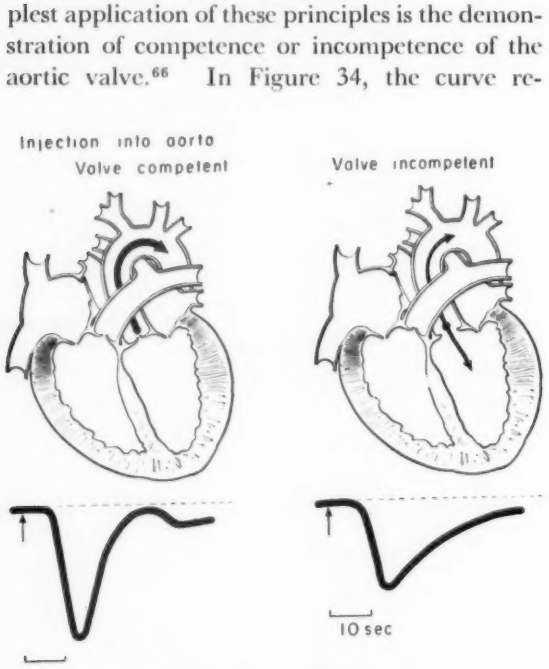

Fig. 34. Localization of valvular regurgitation to the aortic valve. On the left, above, is a diagram of the pathway of dye after injection just distal to a competent aortic valve (catheter advanced retrogradely to this position); below is a normal dye curve recorded from a systemic artery after such injection. On the right, above, is a diagram of the pathways of dye after injection just distal to an incompetent aortic valve; below is the abnormal dye curve recorded from a systemic artery after such injection. The abnormalities of the dilution curve indicative of valvular regurgitation include a diminished peak concentration of dye, prolonged disappearance slope and absence of a systemic recirculation peak.

In Figure 35, the actual curve recorded from the radial artery after injection of dye distal to the aortic valve in a 45-year-old man with severe aortic regurgitation (top curve) is compared with a similar curve recorded from a 44-year-old man with mild aortic regurgitation (bottom curve). The upper curve is characterized by pronounced disproportionate prolongation of the disappearance slope and absence of a recirculation peak. The abnormalities in the lower curve, however, are less severe. There is disproportionate prolongation of the disappearance slope, but the recirculation peak is present, occurring approximately 34 seconds after the peak concentration.

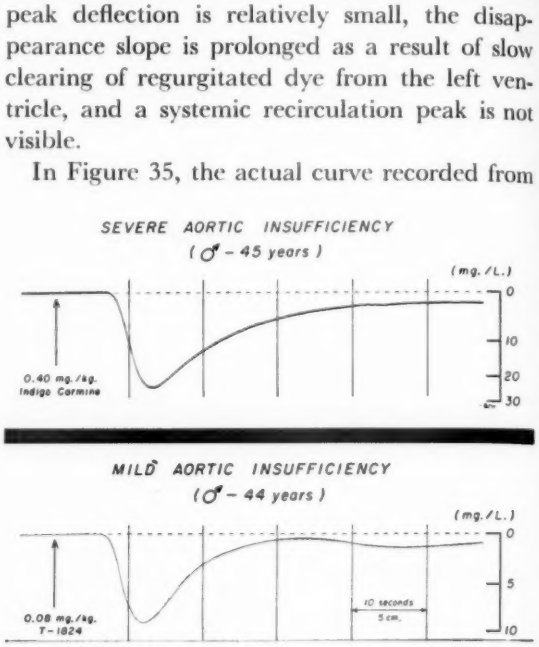

Fig. 35. Demonstration of aortic regurgitation by indicator-dilution curves. Above is an abnormal dye-dilution curve recorded from the radial artery after injection of dye just distal to the aortic valve in a 45-year-old man with aortic stenosis and severe aortic regurgitation. The great prolongation of the disappearance slope and the absence of a recirculation peak are diagnostic of aortic regurgitation in the absence of a left-to-right shunt at or distal to the aortic valve. Below is a similar curve recorded from a 44-year-old man with aortic stenosis and mild aortic regurgitation (diagnosis confirmed at operation). In contrast to that above, the disappearance slope of this curve is only slightly prolonged. A recirculation peak is readily identified and occurs approximately 34 seconds after the peak concentration.

The aortic valve, the most distal of the four heart valves in the pathway of blood flow, is unique by virtue of its position in that a single injection distal to the valve can demonstrate its competency or incompetency, provided the presence of a left-to-right shunt from the aorta has been excluded. However, when dye is injected between two valves, for example, into the right ventricle, the curve recorded at a peripheral arterial site, if it is of a normal contour, not only suggests that the proximal (tricuspid) valve is competent but also demonstrates that all the valves in the pathway of blood flow distal to the injection are competent. If, however, the curve indicates valvular regurgitation, then one or more of the valves distal to the injection site may be incompetent.

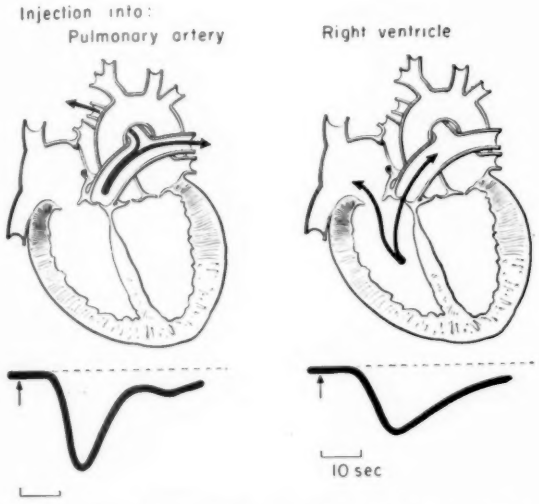

Fig. 36. Localization of valvular insufficiency to the tricuspid valve. On the left, above, is a diagram of the pathways of the dyed blood after injection of indicator into the pulmonary artery in tricuspid insufficiency. The dilution curve (below) recorded at the radial artery is normal, indicating that the pulmonary, mitral, and aortic valves are competent. On the right, above, is a diagram of the pathways of the dye after injection into the right ventricle in tricuspid insufficiency. The dilution curve recorded at a systemic artery (below) demonstrates the abnormalities produced by valvular regurgitation. Comparison of these two curves localizes valvular insufficiency to the tricuspid valve.

To localize the regurgitation, it is necessary to record a curve of normal contour after injection of dye just distal to the first competent valve that lies distal to the incompetent valve, followed by a second abnormal curve recorded after injection between the competent valve and the incompetent one.

Demonstration of Tricuspid Regurgitation: This is illustrated diagrammatically in Figure 36, showing localization of valvular regurgitation to the tricuspid valve. On the left, the contour of the peripheral curve (below) recorded after injection of dye distal to the pulmonic valve is normal. The curve recorded after injection into the right ventricle (right, below) shows the abnormalities caused by valvular regurgitation described above, thus localizing regurgitation to the tricuspid valve.

An example of the application of this technic to the localization of tricuspid regurgitation despite the presence of a left-to-right shunt through a patent ductus arteriosus is shown in Figure 37. In this patient, the smaller deflection and more severely prolonged disappearance slope of the curve recorded after injection into the right ventricle (and the superior vena cava) compared to the curve recorded after injection into the pulmonary artery are so pronounced that the diagnosis of tricuspid regurgitation is established.

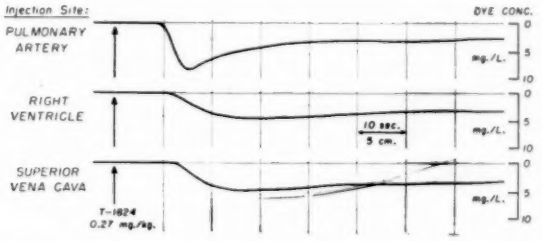

Fig. 37. Arterial dilution curves demonstrating tricuspid insufficiency in a 15-year-old girl with patent ductus arteriosus and pulmonary hypertension. Arterialization in the pulmonary artery demonstrated the presence of a left-to-right shunt through the ductus. The prolonged disappearance slope and absence of a systemic recirculation peak noted in the record from the radial artery after injection into the pulmonary artery (top curve) are independent evidence of the left-to-right shunt. In addition, the smaller deflections and more severely prolonged disappearance slopes of the curves recorded after right ventricular and superior vena caval injections are so pronounced that the diagnosis of tricuspid insufficiency is established.

Use of Two Sampling Sites: The use of two sampling sites to localize an incompetent valve

is illustrated in Figure 38. This diagram schematically represents localization of aortic regurgitation during combined catheterization of the right and left sides of the heart. The dye was injected into the pulmonary artery and dilution curves were recorded simultaneously at the left atrium and radial artery. The normal contour of the curve recorded at the left atrium indicated that both the pulmonary and the mitral valves were competent. Because of aortic regurgitation, the dye was cleared slowly from the left ventricle so that the curve recorded at a systemic artery showed the abnormalities produced by valvular regurgitation, thus localizing regurgitation to the aortic valve.

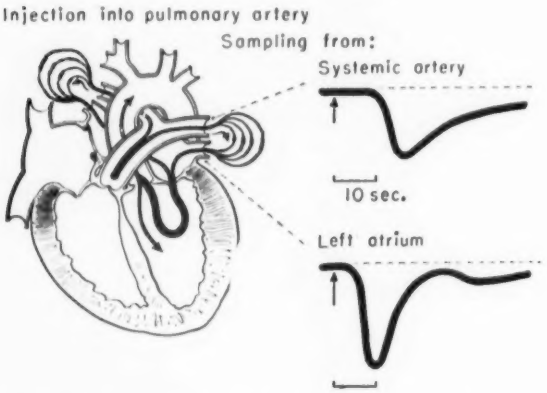

Fig. 38. Localization of regurgitation to the aortic valve by dilution curves recorded simultaneously at sites proximal (left atrium) and distal (radial artery) to a competent mitral valve during combined catheterization of the right and left sides of the heart. After injection of dye into the pulmonary artery, a normal record from the left atrium (lower curve) indicates that both the pulmonary and the mitral valves are normal. The abnormal curve (top) recorded from a systemic artery indicates incompetency of the aortic valve, the presence of a left-to-right shunt having been excluded by catheterization data.

In Figure 39, the actual curves recorded from the left atrium and the radial artery during catheterization of the left side of the heart in a 44-year-old man with aortic regurgitation are superimposed. The left atrial curve is essentially normal, but the abnormalities of the curve recorded at the radial artery localize regurgitation to the aortic valve. This patient died as a result of congestive heart failure several weeks after this study. This diagnosis was confirmed at necropsy.

The routine use of these technics during catheterization of the right side of the heart and combined catheterization of the right and left sides of the heart and the aorta is an essential part of cardiac catheterization. Addition of these and other auxiliary technics during catheterization of the heart considerably increases the diagnostic success of such a study and diminishes the likelihood of unrecognized hemodynamic alterations that might prove of vital importance in the successful treatment of the patient.

Comment and Summary

A large number of methods of differentiating patients with predominant mitral stenosis from those with predominant mitral regurgitation have been described that are based on analysis of pulmonary artery wedge, left atrial and left ventricular pressure pulses or of indicator-

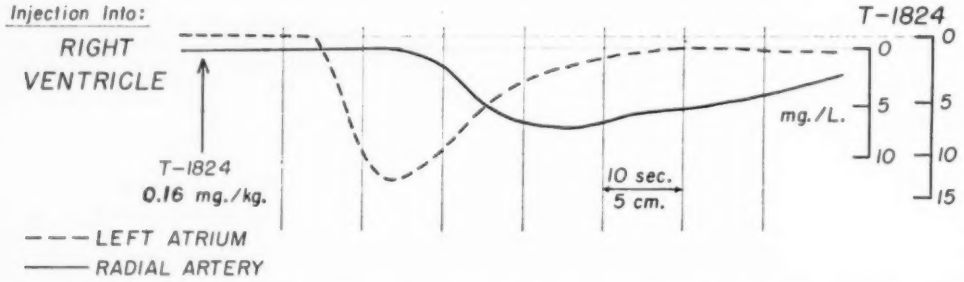

Fig. 39. Demonstration of aortic insufficiency in a 44-year-old man with combined aortic stenosis and aortic insufficiency by dilution curves recorded simultaneously at the left atrium and the radial artery. The left atrial curve (broken line) superimposed on the radial curve (solid line), although prolonged in all components, does not indicate severe valvular regurgitation. However, the curve recorded at the radial artery has a reduced deflection and a disproportionate prolongation of the disappearance slope, thus identifying the aortic valve as the site of regurgitation. The diagnosis in this patient subsequently was confirmed by necropsy.

dilution curves recorded from various sites in the circulation after injection of an indicator dye at selected sites in the systemic or venous circulation. Some degree of discrimination between mitral stenosis and mitral regurgitation is provided by all these methods. This differentiation has been demonstrated to be rather good, particularly for some of the indicator-dilution technics. Unfortunately, however, none of the methods devised up to the present provides a completely uniform separation of patients with predominant stenosis from those with predominant regurgitation.

It is of value to review the possible reasons for the occasional errors in this differentiation. Almost certainly some may not be true errors but may stem from incorrect categorization of these patients on the basis of the findings of the surgeons during palpation at operation, the clinical data and the results of catheterization of the right and left sides of the heart. From this point of view, a study of dilution curves recorded in an animal preparation[78] in which the parameters of forward and regurgitant flow can be controlled and continuously recorded would be of great value. On the other hand, from the practical viewpoint, if at operation the experienced surgeon encounters such a severe degree of regurgitation that he is certain that improvement in the hemodynamic status cannot be accomplished by attempting relief of the degree of narrowing of the valve which may exist, this patient should not have been selected for operation and, therefore, it must be concluded that the methods used for this selection have failed. In any event, the lack of other independent methods for assessment of the degree of valvular regurgitation in human beings forces one to assume that the categorization arrived at by a combination of clinical, cardiac-catheterization and surgical findings is correct and to attempt to devise methods that give the best possible differentiation of the categories so selected.

The possibilities for development of a single physiologic method that will provide the desired degree of uniform differentiation do not appear bright because of the existence of uncontrollable factors such as variations in compliance of the left atrium in reference to left atrial pressure pulses and, in reference to indicator-dilution technics, the non-uniform mixing of injected or regurgitant indicator, the striking effects of variations in the volume and degree of mixing of dye regurgitated or injected into the chambers upstream and downstream to an incompetent valve, and the minimal distortion of dilution curves (which may escape detection in spite of severe regurgitation) when the cardiac chambers are small and the blood flow high.

It is worthy to note that many of the hemodynamic methods based on left atrial or pulmonary artery wedge and left ventricular pressure pulses, as well as on indicator-dilution technics, utilize parameters that are distorted in a more or less independent manner by valvular regurgitation. This is an ideal situation for the application of multiple-variant types of analysis[37] (Fig. 23) in order to improve the degree of discrimination over and above that attainable by analysis of one variable alone. Promising results have been attained with this method of attack.[79]

Based on the degree of success that has been attained in differentiating instances of predominant stenosis from predominant regurgitation in patients with mixed defects of the mitral valve by the use of only one physiologic variable, it is logical to presume that a relatively high degree of success will be attained in this difficult differential diagnostic problem when methods are developed to utilize, in a properly weighted fashion, multiple variables, including physiologic data as well as clinical data that can be obtained reproducibly on the same patient by different clinicians.

Acknowledgments

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This concludes Part I of the Symposium on Mitral Regurgitation. Parts II and III will be published in the August and September issues.

Clinical Studies

Phenprocoumon (Marcumar)*

I. An Agent for Short-Term Anticoagulant Therapy

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THE TREATMENT of acute thromboembolic accidents by controlled short-term anticoagulative therapy has gained widespread acceptance.[3–5,7,8,10,16,17] However, no generally available oral anticoagulant is entirely satisfactory; therefore evaluation of recently developed anticoagulants must continue.

Promulgated criteria[5] for the ideal oral anticoagulant should be modified. The anticoagulant should ideally affect a minimum of the components of the blood clotting mechanism consonant with a consistently demonstrable anticoagulative effect. In 1953 Koller and Jakob[13] reported that prothrombin and Factor VII can be easily maintained at a constant level with 3-(1′-phenylpropyl)-4-hydroxycoumarin. Extensive data regarding this drug, also known as marcumar (generic designation phenprocoumon), have appeared in the European literature, but there have been few reports on experiences with this compound in the American and English literature. As a consequence, phenprocoumon is little known in this country.

This report will concern itself with our experience with phenprocoumon as an agent for short-term anticoagulant therapy.†

CASE MATERIAL

One hundred and sixty hospitalized patients, 119 males and 41 females, received short-term anticoagulant therapy with phenprocoumon.‡ Their age and sex distribution and diagnoses are given in Table I. Twenty-six cases of the total series were excluded from evaluation because the patient had either been given oral anticoagulants before phenprocoumon was instituted, or had concomitant heparin therapy, or had less than six prothrombin time assays. Thus, 134 patients were evaluated.

TABLE I

Sex, Decade of Life, and Diagnosis

Sex	
Male	119
Female	41
Decade of life	
4th	4
5th	25
6th	59
7th	54
8th	15
9th	3
Conditions treated by anticoagulant therapy	
Infarction of the myocardium	93
Coronary artery insufficiency	36
Simple phlebothrombosis	8
Phlebothrombosis with pulmonary embolism	6
Chronic atrial fibrillation	6
Cerebral artery occlusion	6
Cerebral artery insufficiency	5

* From the Department of Internal Medicine, Division of Cardiology, Henry Ford Hospital, Detroit, Michigan.

† Phenprocoumon (Marcumar®). II. An Agent for Long-term Anticoagulant Therapy, will be published at a later date.

‡ Phenprocoumon (marcumar) was supplied in scored 3-mg tablets and in ampules containing 10 mg in 0.2 cc with diluent ampules, through the courtesy of Dr. Leo A. Pirk of Hoffmann-La Roche, Inc., Nutley, New Jersey. (Only the tablets were used in this study.) Phenprocoumon is marketed in the United States under trade name liquamar (Organon).

tients constitute the case material for the analytical considerations.

General Methods

Members of the anticoagulant therapy service of the Division of Cardiology supervised the administration of the anticoagulant. Prophylactic and therapeutic levels of hypocoagulability were recognized, and shall be specifically delineated below. Maintenance of therapeutic levels of hypocoagulability was attempted in the majority of cases. In the remainder of the patients, the original intention was the attainment and maintenance of prophylactic levels of anticoagulant therapy. Once instituted, anticoagulative therapy was usually continued throughout hospitalization. Within 10 to 14 days, or at such later time as the patient became ambulatory, the level of hypocoagulability was allowed to rise toward prophylactic levels.

Prophylactic levels are considered to have been attained when the prothrombin complex time is between 20 and 25 sec. Such levels offer the patient moderate protection against thromboembolic accidents. They are employed routinely in long-term anticoagulant therapy, and are frequently maintained toward the termination of short-term anticoagulant therapy as has been pointed out above.

Prothrombin complex times of 25 to 35 sec must be attained before therapeutic levels of hypocoagulability are considered to have been reached. These levels offer the maximum amount of protection against thromboembolic episodes, while simultaneously minimizing the risk of complications due to hypocoagulability. They are routinely utilized during the acute phase of treatment of thromboembolic accidents. However, such levels are not intentionally induced unless very close supervision of the patient can be maintained.

The determination of the prothrombin complex time, hereafter referred to as the prothrombin time, was routinely accomplished by the Quick one-stage technic. Control times were determined daily. Warner-Chilcott diagnostic plasma and normal fresh human plasma were sources for normal prothrombin complex. Difco rabbit brain thromboplastin, yielding a control time of 12 to 15 sec and freshly prepared daily, served as the source of tissue thromboplastin. Calcium ion was obtained from 0.025 molar calcium chloride. With these components our control times were usually 14 sec and this may be assumed for determining percentages of prothrombin. The prothrombin time of patients receiving anticoagulant therapy was determined with plasma obtained without regard to the fasting state. The test was usually performed within three hours of withdrawal of the test specimen.

The authors feel that no little confusion has arisen from the practice of expressing the results of the Quick prothrombin time as percentages. Discourse regarding this matter would be out of place in this report, but prothrombin times shall be reported in seconds.

Methods for determining the effects of phenprocoumon on autoprothrombin I (Factor VII, Stabile Factor) and autoprothrombin II (PTC, Christmas Factor or Factor IX) have been reported in detail elsewhere[12] and will not be recorded here.

The loading dose of phenprocoumon was administered as soon as the decision to use anticoagulant therapy was transmitted to the service. An initial prothrombin time was obtained prior to administration of the loading dose. However, since this initial time was within the normal range if the patient received anticoagulative therapy it will not be considered here. The "first" prothrombin time was obtained at 8:00 a.m. the morning following the administration of the loading dose. Since no constant time relationship exists between the loading dose and the "first" prothrombin time an average time lapse of 16 hours is assumed. Subsequent prothrombin times were taken

TABLE II

Division of 134 Patients According to Loading Dose

Group	Number of patients	Loading dose (mg)
A	21	21
B	24	30 or 26
C	53	42 or 45
D	33	51
E	3	72

TABLE III

Responses of 134 Patients Receiving Different Initial Doses of Phenprocoumod (Marcumar)

Group (Initial marcumar dose)	Prophylactic responses (prothrombin time 20–25 sec)			Therapeutic responses (prothrombin time 25–35 sec)		
	Number of patients	Average		Number of patients	Average	
		Total marcumar dose (mg)	Time of onset of prophylactic response (hr)		Total marcumar dose (mg)	Time of onset of therapeutic response (hr)
A (21 mg)	21	32.5	64	11	50.4	136
B (30 or 36 mg)*	24	41.5	40	19	50.0	64
C (42 or 45 mg)*	53	51.5	40	50	56.0	64
D (51 mg)*	33	56.5	40	31	66.0	64
E (72 mg)	3	72.0	16	3	72.0	40
Total	134†			114		

* The average initial marcumar dose of the 110 patients in Groups B, C and D was 44 mg.

† Twenty of these 134 patients who reached the prophylactic zone were not intended to be taken to the therapeutic zone.

daily at 8:00 a.m. and subsequent doses of phenprocoumon were administered at 8:00 p.m. each day.

The 134 patients can be divided into five unequal groups based upon the loading dose administered to each patient, as can be seen in Table II. This division facilitates the study of the response to the loading dose of phenprocoumon. This study is based on the time interval which transpired between loading dose and arrival at the prophylactic level and later the therapeutic level of hypocoagulability. Loading dose size was increased in an effort to shorten this response interval. In passing it should be noted that the patients in group A received a standard second dose of 9 mg. In the remainder of the patients the second dose was left to the discretion of the controlling physician. It could not be demonstrated that the size of the second ration of phenprocoumon as administered during this study, not more than 9 mg, exerted a significant effect on the response interval and will not be considered in this report.

When prothrombin times in excess of 35 sec were reported on two consecutive days or when such values were obtained several days apart with intervening values of no less than 35 sec, treatment was considered to have produced too marked a depression of the blood clotting mechanism. For brevity this excessive prolongation of the prothrombin time shall be designated as "overshooting." When overshooting occurred within five days of initiation of anticoagulative therapy it was adjudged due to the loading dose. When this undesirable effect occurred later in the course of treatment it could usually be related to the over-ambitious application of the anticoagulant.

Since 2-methyl-3-phytyl-1,4-naphthoquinone (vitamin K_1) promptly corrects excessive hypocoagulability from oral anticoagulant therapy, this agent was employed for reversing the effects of phenoprocoumon whenever bleeding was thought to be potential or actually had occurred. The products used were Mephyton® and konakion (generic designation phytomenadione).*

* Five mg mephyton tablets were supplied by Sharp & Dohme, Division of Merck & Co., Inc. Konakion was made available through the courtesy of Dr. Leo A. Pirk of Hoffmann-La Roche as a 2 per cent drop solution and in 1 ml ampules, 10 mg/ml.

The plan was to give, in general, the following doses by the routes indicated: 5 to 10 mg orally, if unduly prolonged prothrombin times were to be corrected; 25 to 50 mg orally or intravenously, depending on circumstances, for interruption of anticoagulant therapy prior to surgery; 25 to 50 mg intravenously, if possible, supplemented by such doses orally, to combat the emergency of severe bleeding; and smaller doses, preferably by mouth, if the hemorrhagic episode was of a minor nature.

Results

Prothrombin Responses to Different "Loading" Doses of Phenprocoumon: As is seen in Table III, the greater the "loading" dose of phenprocoumon, the shorter was the time interval between institution of treatment and the onset of prophylactic responses. Thus, with an initial dose of 21 mg it took 64 hours before the prothrombin time values reached the prophylactic zone. (The average total dose of phenprocoumon at that time was 32.5 mg.) However, with an initial phenprocoumon dose of 72 mg† a prophylactic response was attained in 16 hours.

Similarly, a "loading" dose of 21 mg produced therapeutic prothrombin time values 136 hours after institution of medication (the average total dose of phenprocoumon at that time was 50.4 mg), but it took only 40 hours to obtain comparable effects with a "loading" dose of 72 mg. Furthermore, it appears from Table III that all 110 patients who received "loading" doses ranging from 30 to 51 mg (average 44 mg) reached prothrombin time values in the prophylactic range within an average of 40 hours. (The average total phenprocoumon dose at that time was 51 mg.) Also, the prothrombin times of all 100 of these patients taken to therapeutic levels arrived in this zone after an average of 64 hours. (The average total phenprocoumon dose at that time was 58 mg.)

Figure 1 is a scatter graph showing the daily prothrombin responses of 50 patients randomly selected from the aforementioned 100 cases. Of all daily prothrombin time determinations carried out for these 50 patients, 90 per cent were within the prophylactic or therapeutic zone. After therapeutic levels had been reached, these 50 subjects received an average daily phenprocoumon ration of 3.5 mg. The average prothrombin time value resulting during the subsequent 11 days of daily determinations was 28 sec. A total of 558 prothrombin time determinations were carried out for these patients after they had reached the therapeutic zone. Only 78 of the values thus obtained were below 25 sec. Thus, therapeutic levels as reflected by the prothrombin time, were maintained for 86 per cent of this time. The great stability of the desired depression of the blood coagulation mechanism is reflected in the flatness of the curve portraying the average prothrombin time values in Figure 1.

Effects on Prothrombin, Autoprothrombin I and Autoprothrombin II: Johnson *et al.*[12] utilizing serum and plasma samples obtained from 10 patients taken to therapeutic levels and included in this report, studied the effects of phenprocoumon on the separate factors prothrombin, autoprothrombin I and autoprothrombin II. These data are reported in detail elsewhere, but shall be reviewed here.

The fall of prothrombin content, as measured by the two-stage prothrombin determination, was delayed. There was little change in concentration the first day and only about one-half of the cases demonstrated a change by the second. However, by the third day prothrombin levels had decreased by as much as 75 per cent. These depressed levels were consistently maintained throughout the remaining treatment period.

An immediate and drastic decrease in both serum and plasma levels of autoprothrombin I (Factor VII) was demonstrable following administration of phenprocoumon. This depletion was maintained throughout the period of anticoagulant administration. The initial increase in the Quick prothrombin time is probably due to the decreased concentration of this factor.

Using the difference between the plasma cofactor assay and the serum cofactor assay as an index of the concentration of autoprothrombin II (Factor IX, PTC, Christmas Factor) no decrease could be demonstrated. This lack of

† Although hemorrhagic complications and excessively high prothrombin time values were not encountered in these three patients, the administration of a single phenprocoumon dose of 72 mg is not recommended.

effect on autoprothrombin II had been predicted previously but had not been proven.

Undesirable Effects: "Overshooting" occurred in 22 of the 160 patients treated with phenprocoumon, an incidence of 13.7 per cent. Sixteen cases were observed within five days of the initiation of anticoagulant therapy. Six cases occurred later in the course of treatment. The 16 cases of overshooting due to the initial phenprocoumon dose were distributed as follows: two cases in group B, eight cases in group C and six cases in group D. These numbers correspond to 8.3 per cent, 15.1 per cent and 18.2 per cent of the patients included in these three groups. Since overshooting did not occur in the patients of group A, it is obvious that the higher the initial dose, the greater the likelihood that overshooting will be encountered. Because bleeding is the most dreaded complication of overshooting it is interesting to note that in the 16 patients who showed excessively high prothrombin time values due to the loading dose, bleeding did not occur. There were, however, two cases of hemorrhage among the six patients who developed extensive hypocoagulability later in the course of treatment. These cases of hemorrhage shall be discussed with other cases of hemorrhage (vide infra).

Hemorrhagic Complications of Anticoagulant Therapy: The precise property of oral anticoagulants allowing their utilization as therapeutic agents also makes them potentially dangerous. Hemorrhage, as a complication of anticoagulant therapy, is not infrequently encountered. This complication may result as a sine qua non of anticoagulative therapy or from magnification of hemorrhage due to an unsuspected disorder. In either event this unwarranted complication is of serious mien. It would be difficult to report a series of unselected patients treated at therapeutically effective levels without including occasional hemorrhagic complications; this series is no exception.

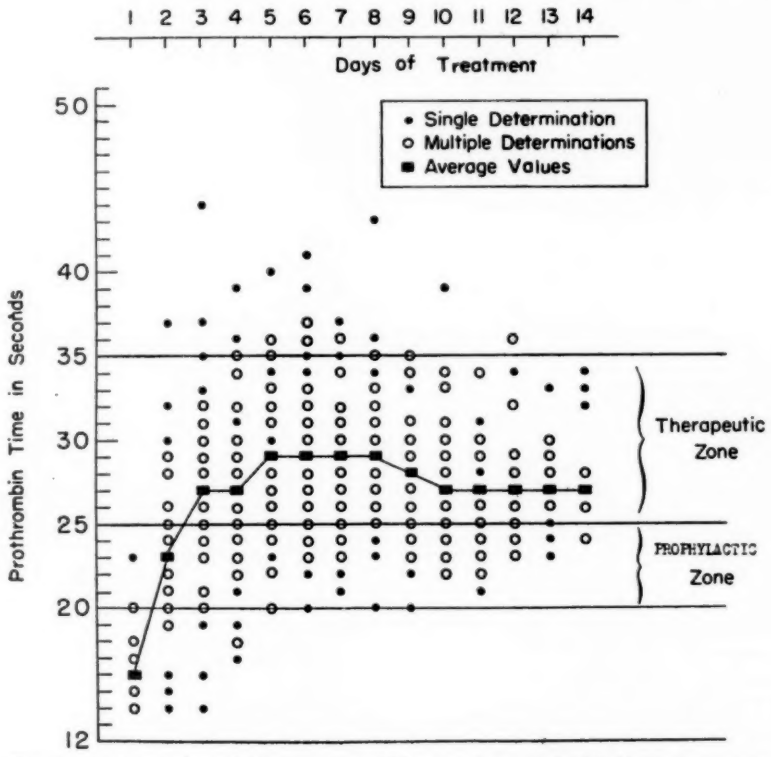

Fig. 1. Daily prothrombin responses of 50 patients treated with phenprocoumon (marcumar).

Six cases of hemorrhagic complications were encountered, an incidence of 3.75 per cent. Four cases were of a minor and two of a major

nature. Of the former, three cases of macroscopic hematuria were encountered. The remaining case was one of gingival hemorrhage. One hemorrhage of major consequence was from an operative site, the other was manifested by hematemesis.

The character of the minor hemorrhagic complications exhibited the following essential features. In one instance blood appeared in the urine during a late overshoot. In the other two cases of hematuria the prothrombin times were 27 and 25 sec, respectively. In one of these latter cases there was a concomitant cystitis. Phenprocoumon was temporarily discontinued in all three instances. In addition, one subject was given 5 mg of vitamin K_1 orally. The hematuria stopped promptly in all three patients. The gingival hemorrhage occurred in a patient whose prothrombin time was 40 sec. Following 5 mg of orally administered vitamin K_1 the hemorrhage was controlled. In none of these 4 patients was there significant blood loss.

The following circumstances are relevant to the histories of the two cases with major hemorrhagic episodes. The first patient had sustained a myocardial infarct during surgery for an anal fissure. Three days after the operation anticoagulant therapy was instituted. On the fourth day of treatment, when the prothrombin time was 25 sec, bleeding occurred from the operative site. This hemorrhage was controlled by 10 mg of vitamin K_1 given intravenously and the patient made an uneventful recovery.

The second patient, receiving anticoagulant therapy for a myocardial infarct, had a hematemesis on the twentieth day of treatment when his prothrombin time was 30 sec. Five mg of vitamin K_1 given intravenously reduced the prothrombin time to 19 sec, but hematemesis recurred. Five mg of Vitamin K_1 were repeated. Although there was no further evidence of bleeding, the patient expired suddenly two days after the first hemorrhagic episode. Autopsy revealed a thrombosed gastric vein with bleeding from the proximal portion. Thus, in this series of 160 patients there was one fatality due to a bleeding episode—an incidence of 0.625 per cent.*

Thromboembolic Complications of Anticoagulant Therapy: Thromboembolic phenomena may or may not constitute failure of anticoagulant therapy. Existing thrombi may serve as a nidus of emboli regardless of effective anticoagulative therapy, and such cases should not be considered, in their strictest sense, as failures. However, the occurrence of any thromboembolic episodes while under the influence of anticoagulants is of prime interest. Therefore, we consider it noteworthy that no such complications or evident failures of therapy occurred in this series.

Effectiveness of Vitamin K_1: Vitamin K_1, which was mostly given orally and sometimes in divided doses, was used in 11 instances. As is seen in Figure 2, the following doses of vitamin K_1 were used: 2 mg in one patient; 5 mg in four instances; 10 mg in three cases, one of which received two 5 mg doses; 15 mg in three equally divided doses, given 24 hours apart, in one patient; 25 mg in one case; and, finally 100 mg in one instance. The prothrombin time findings on the day prior to the administration of vitamin K_1 are plotted in the graph directly below the prothrombin time values recorded on the day vitamin K_1 was given. The effects of this antagonist on prothrombin times are also indicated. It is obvious that vitamin K_1 was a reliable agent for reversing hypocoagulability in all cases. Hypercoagulability of the blood was not produced and refractoriness to further anticoagulant therapy did not occur.

Discussion

Results reported herein and results promulgated by other investigators are reasonably uni-

* There was another patient, not included in this series on short-term anticoagulant therapy, who had a fatal hemorrhagic episode and is mentioned here only because bleeding occurred during one of her periods of hospitalization. She was a young woman with severe hypertension who, after her third myocardial infarct, was placed on long-term anticoagulant therapy. Four months later she developed hemiplegia of her right side. The prothrombin time was 19 sec and after consultation with a staff neurologist, anticoagulant medication was continued because it was thought that the patient had a cerebral thrombosis. There was improvement for five days, but on the sixth day the patient suddenly went into a coma and death occurred in a few hours. Autopsy revealed a hemorrhage into the left ventricle and the right brain stem. This case will be included in our later report on long-term anticoagulant therapy.

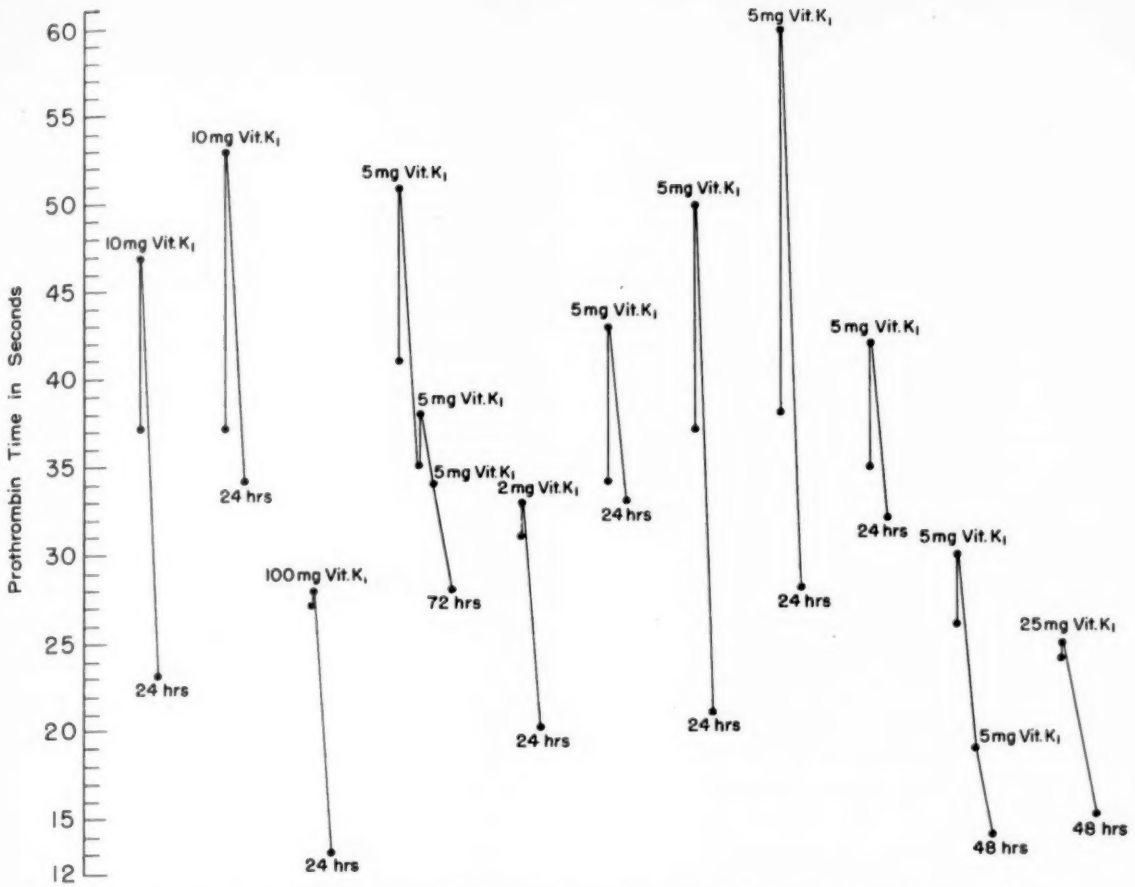

Fig. 2. Effect of vitamin K_1 (mephyton or konakion) on prothrombin times prolonged by phenprocoumon (marcumar).

form, although correlation is not exact due to the different experimental designs of the several investigators. Nevertheless, it is interesting and instructive to consider these accumulated results simultaneously.

Loading Dose: Koller and Jakob,[13] as well as several other investigators,[2,3,6,14–16] noted an adequate or maximal increase in prothrombin time within 36 to 72 hours of administration of a loading dose of 21 mg with or without a second day's ration of 9 mg. An initial increase in prothrombin time was noted by many of these investigators within 18 hours of initial administration. In our series an average lapse of 64 hours was required to reach prophylactic levels and only after 136 hours were therapeutic levels attained when a similar loading dose was given. However, an initial increase in prothrombin time could be noted within 18 to 24 hours. Because of the various methods and component materials employed to determine the prothrombin time it is hazardous to assume an exact parallelism between published prothrombin times. Nevertheless, this delay in attaining prophylactic or therapeutic levels was undesirable. Therefore, larger quantities of phenprocoumon were employed as loading doses.

Toohey[15] has reported two series of patients receiving 24 and 30 mg as a loading dose. In each series the desired therapeutic levels were reached after a shorter lapse of time than that interval observed after 21 mg loading dose. In point of fact, 66 per cent of the series receiving 30 mg loading dose achieved therapeutic levels after 36 hours. However, undesirably prolonged levels of hypocoagulability occurred in a sufficient number of cases receiving 30 mg for Toohey to suggest the dosage was excessive. Brambel,[3] employing a loading dose of 30 mg, was able to induce desirable hypocoagulability

in 38 hours and was inclined to favor 30 mg as the optimal loading dose. However, when Brambel employed 40 mg as a loading dose he noted a greater number of patients exceeded the maximum level of desirable hypocoagulability. We have employed various loading doses from 30 to 51 mg. There was no significant difference in response to these doses. Prophylactic levels were attained within 40 hours on the average and therapeutic levels were demonstrated after 64 hours. Thus, by increasing the loading dose the induction period could be brought into the "mid-range" of other oral anticoagulants. As had been previously reported by Toohey and Brambel, increasing the size of the loading dose was attended by an increase in the incidence of overshooting. However, it should be noted that no serious untoward complications of overshooting were encountered. Therefore, overshooting would seem an acceptable risk in view of the shortened induction period.

Maintenance Dose: Previous investigators agree that a maintenance dose of from 1.5 to 9 mg is usually required. The ration noted herein is not significantly different being 2.5 to 9 mg with an average of 3.5 mg.

Stability of Hypocoagulability: Anticoagulant therapy is predicted upon the physician's ability to produce and maintain a controlled state of hypocoagulability by interfering with various components of blood upon which coagulation is dependent.[9,11] The efficacy and reliability of an anticoagulant must be judged by its ability to induce such an effect and maintain this effect with a high degree of stability. Several drugs will interfere with one or more of the components of blood coagulation sufficiently to produce a state of hypocoagulability. However, this action is so evanescent as to preclude the drug's employment for anticoagulant therapy.

Investigators reporting their experience with phenprocoumon have repeatedly noted the ease with which desirable levels of hypocoagulability were maintained. Prior[14] reported that after the third day of drug administration only 1 per cent of the prothrombin values were below the desired level. Brunton[6] observed such values in only 3.2 per cent of 500 prothrombin time determinations. In Brambel's[3] series the prothrombin times of treated patients were within the desirable range in 85 per cent of the determinations performed after the first 36 hours. This investigator further pointed out that less potent anticoagulants gave only 25 to 40 per cent therapeutic response in his and other investigators' hands. In our series therapeutic results were maintained 86 per cent of the time once such levels were attained. Prophylactic or therapeutic levels were maintained for 90 per cent of the entire treatment period—from loading dose till discontinuation of anticoagulant therapy. As so concisely stated by Brambel, "such conditions are highly desirable and most essential for effective anticoagulant therapy during short-term treatment."

Toohey[15] and Brambel[3] both reported a likelihood of reaching undesirable levels of hypocoagulability as the loading dose of phenprocoumon was increased. In this respect Toohey thought a loading dose of 30 mg or above excessive. Brambel, however, did not note excessive prolongation until he employed a loading dose of 40 mg. In this series we report overshooting following loading doses of 30 mg and above. However, the entire incidence of early overshooting amounted to only 10 per cent of cases treated. In none of these patients did any untoward complication arise during this early overshoot. Late overshooting is always a present danger during anticoagulant therapy. While late overshoots occurred in only 3.8 per cent of this series, 30 per cent of our entire incidence of hemorrhagic complications occurred in this group.

Hemorrhagic Complications: In spite of repeated reports of accrued benefits from controlled anticoagulation,[1,5,7,8,10,16,17] hemorrhage is constantly advanced as the complication invalidating all possible advantages. While this serious complication constitutes a calculated risk of anticoagulant therapy, the authors believe that it has been over-emphasized and present-day experience, selection of patients, and drugs make this complication less important than in the past. A hemorrhagic risk of 10 to 15 per cent is generally accepted as attending anticoagulant therapy. One of the authors[5] reported, in 1955, a series of patients treated with another

anticoagulant in which the over-all hemorrhagic complications were 5.2 per cent. Combining all reported hemorrhagic complications of the several authors[2,3,6,13–16] with prior experience with phenprocoumon, 23 in number, with our own six, a total of 29 cases of 641 patients undergoing short-term anticoagulant therapy have now been recorded in the literature. This is an incidence of 4.5 per cent. Furthermore, this represents only 1.7 per cent of all patients who have received phenprocoumon for either short-term or "ultra-short" term anticoagulant therapy. In view of the repeated warnings of major hemorrhagic complications risked during anticoagulative treatment, it is worthy of notice that such complications occurred in only 0.5 per cent of collected patients receiving phenprocoumon for either "ultra-short" term or short-term anticoagulant therapy.

Thromboembolic Complications: This type of complication was rarely encountered by any investigator reporting experience with phenprocoumon. None were encountered in this series. Nine cases (0.5 per cent) are included in the reviewed literature which, including this series, contains a total of 1,607 patients.

Duration of Action of Drug After Simple Discontinuation: We have made no pertinent observations regarding this matter. Other investigators accept a lapse of 5 to 14 days.

Effectiveness of Vitamin K_1 Counter Therapy: One would not be remiss in stating that the introduction of 2-methyl-3-phyto naphthoquinone, vitamin K_1, has allowed a greater freedom of action to the physician employing oral anticoagulant therapy. Its effectiveness, regardless of route of administration, in countering the induced hypocoagulability has been a large factor in reducing the incidence of hemorrhagic complications of anticoagulant therapy. No oral anticoagulant which was refractive to this counter measure would likely enjoy much popularity. All investigators attest to the effectiveness of vitamin K_1 as a counter measure to phenprocoumon-induced hypocoagulability. Various dosage schedules have been suggested. However, it is generally accepted that 2.5 to 15 mg of vitamin K_1 given orally suffices to return an excessively prolonged prothrombin time to a more desirable level. For more serious complications or pressing needs a larger dose should be administered. A counter effect can usually be detected within three to six hours. We believe that further emphasis on the tailoring of dose size and route of administration should be made, particularly if continuation of anticoagulant therapy is anticipated.

Side Reactions to This Drug Not Related to its Anticoagulant Activity: Only one investigator, Prior,[14] has reported such side reactions to phenprocoumon. One of his patients developed diarrhea which improved upon cessation of administration of the drug. No side reactions of note occurred in the series of patients herein reported.

Summary

One hundred and sixty patients received short-term anticoagulant treatment with phenprocoumon (marcumar).

The effects of different initial doses of phenprocoumon were studied in 134 cases. Phenprocoumon proved to be a potent anticoagulant. Thirty or 36 mg of phenprocoumon produced the desired hypocoagulability of the blood as promptly as an initial dose of 51 mg, when these doses were followed on the second and third day, depending on findings in the Quick test, by doses which ranged from 0 to 9 mg.

After therapeutic levels (prothrombin complex time 25 to 35 sec) had been reached, these were maintained with daily phenprocoumon doses of usually 3 or 4.5 mg. Both low and excessively high prothrombin time values were only rarely encountered with this dosage plan. Thus, in general, the desired depression of the blood clotting mechanism was easily maintained.

The incidence of hemorrhagic complications was 3.75 per cent.

Vitamin K_1 (mephyton or konakion) was an effective antagonist against undue depression of the blood clotting mechanism.

These findings were compared with those reported by the original Swiss workers and by American and British students.

It is concluded that phenprocoumon is an effective agent for short-term anticoagulant therapy and that selected therapeutic prothrombin levels can be maintained with comparative facility.

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Acute Myocardial Infarction in a City Hospital*

II. Experience with Anticoagulants

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THE LITERATURE on the use of anticoagulants in acute myocardial infarction is already voluminous and controversial, and reported experience from large municipal hospitals differs somewhat from that of voluntary institutions. This is a report dealing with the use of anticoagulants in cases of acute myocardial infarction discharged from the University Medical Service (Division II) of Kings County Hospital between July 1, 1954 and June 30, 1955 inclusive. Of a total of 264 such patients, 66 received anticoagulants, while 198 did not receive these drugs. The clinical findings in this total group have been reviewed elsewhere by the authors.[31]

There are three points of view with regard to the use of anticoagulants in acute myocardial infarction: that they should be used routinely, that they should be used selectively, and that they should not be used at all. The first point of view, exemplified by Wright and his colleagues[3,22–29] and also by Loudon[9] and Tulloch and Gilchrist,[6,21] is that the anticoagulants should be employed routinely in all cases of acute myocardial infarction with the exceptions of the following contraindications:

Contraindications to Anticoagulants (Wright)[29]

(1) Prothrombin deficiency (hypoprothrombinemias or potential prothrombin deficiency): Vitamin K deficiency, severe hepatic disease.
(2) Vitamin C deficiency.
(3) Renal insufficiency.
(4) Blood dyscrasias with impairment of the mechanism of hemostasis.
(5) Interruptions of the continuity of the vascular system:
    Surgical operations
    (a) recent operations on the brain or spinal cord;
    (b) recent surgical operations leaving raw surfaces;
    (c) postoperative tube drainage of wounds of viscera;
    (d) operations performed in the presence of obstructive jaundice, external biliary fistula, or severe liver damage.
    Ulcerations and open wounds.
(6) Late pregnancy.
(7) Subacute bacterial endocarditis.
(8) Dissecting aortic aneurysm.

These contraindications are accepted by most, if not all workers. In short, the aforementioned workers subscribe to the routine use of anticoagulants in acute myocardial infarction for the following reasons: (1) reduction in the number of deaths by about one-third, (2) decrease in the number of thromboembolic complications by about one-half, (3) minimal risk in their use, and (4) difficulty in separating "good risk" and "poor risk" cases.

The second point of view, represented by Russek and Zohman,[11–19] Kerwin,[8] and Furman,[5]

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is that the anticoagulants should be used selectively in acute myocardial infarction. These authors favor the administration of such drugs in so-called "poor risk" cases alone. The following are the criteria for this prognostic category as determined within the first twenty-four hours of hospitalization:

Criteria for Poor Risk (Russek et al.)[11–19]

(1) Previous myocardial infarction.
(2) Intractable pain.
(3) Extreme degree or persistence of shock.
(4) Significant enlargement of the heart.
(5) Gallop rhythm.
(6) Congestive heart failure.
(7) Auricular fibrillation or flutter, ventricular tachycardia or intraventricular block.
(8) Diabetic acidosis, marked obesity, previous pulmonary embolism, thrombophlebitis (past or present), polycythemia or other states predisposing to thrombosis.

Russek and Zohman contend that since the preventable mortality of "good risk" cases is quite low (about one per cent) and is frequently less than that arising from the use of the anticoagulants (0.25 to 10 per cent), these agents should be employed only in the so-called "poor risk" cases. According to these workers, the mortality rate in the latter group is 60 per cent.

The third point of view, held by Rytand,[10] Schnur,[20] and Evans,[4] is that the anticoagulants should not be employed in acute myocardial infarction, or at least that it has not been shown conclusively that they are beneficial in this condition. Various criticisms[10,20] are made of the study by the American Heart Association. Also pointed out is the difficulty of evaluating any therapeutic measure in so variable a disease as myocardial infarction. These observations notwithstanding, Schnur[20] offers this final conclusion: ". . . in the more seriously ill patients the theoretic advantages of anticoagulant therapy justify this statement even though there may be some question as to whether its value has been clearly demonstrated."

Another approach to the use of these drugs is that of Halpern *et al.*[7] This group documented a change in prognosis with regard to "good risk" and "poor risk" in the first 48 hours in 29 per cent of 107 cases. They suggested, therefore, that anticoagulants be employed for at least the first two days and then discontinued in "good risk" cases at the end of this period of time.

Methods and Materials

All case records of patients discharged from the University Medical Service (Division II) of Kings County Hospital between July 1, 1954 and June 30, 1955, inclusive, were reviewed. Cases signed out as "old," "probable," or "possible" myocardial infarction were not considered. Out of a total of 394 patients signed out as acute myocardial infarction, only 264 satisfied at least one of the following criteria: (1) demonstration at autopsy of the disease, (2) classic electrocardiographic findings, (3) a clinical picture compatible with the diagnosis of acute myocardial infarction, preceded by a history of coronary arterial disease and followed by fever (rectal temperature over 100° F), leukocytosis (over 10,000 WBC per cubic millimeter), or increase in the proportion of neutrophiles in the differential count (70 per cent or greater), or elevation of the corrected erythrocyte sedimentation rate* (over 10 mm/hr in males and over 20 mm/hr in females) not explained on any other basis.

Observations

Of the 264 cases, 66 or 25 per cent received anticoagulants while 198 or 75 per cent were untreated. Hereafter, the designations treated and untreated will be used synonymously with the group receiving and the group not receiving anticoagulants, respectively. Administration of anticoagulants was determined by the preference of the attending physicians and not in accordance with any organized program. It is

TABLE I
Method of Administration of Anticoagulants

Anticoagulant	Number
Heparin with or without dicumarol	36
Heparin alone	9
Dicumarol with or without heparin	57
Dicumarol alone	30

* Wintrobe method.

notable that 88 per cent of the treated group were in the "poor risk" category. The majority of the treated group received dicumarol, either with or without heparin, but nine patients received heparin alone (Table I).

Heparin (aqueous) was given by the intravenous or deep intragluteal intramuscular route in doses of 50 to 100 mg every four to six hours. Clotting times were measured by the standard Lee-White method, and heparin was employed usually at the initiation of anticoagulant therapy to achieve rapidly a prolongation of clotting time to two to two and one-half times the pretreatment value.

Bishydroxycoumarin (dicumarol) was administered orally in doses of 200 to 300 mg the first day, 100 to 200 mg the second day, and 25 to 100 mg on subsequent days, depending on prothrombin levels. Prothrombin times were maintained in the range of 25 to 30 seconds, as measured by the Quick one-stage method. Patients receiving anticoagulants after the first week of hospitalization for some complication, e.g., phlebitis, are not included in this report.

Table II summarizes the mortality of patients receiving heparin alone, dicumarol alone, and heparin and dicumarol combined. There was no important difference between the mortality of the patients receiving dicumarol alone (23.3 per cent) and dicumarol and heparin combined (29.6 per cent). The nine patients who received heparin alone constituted too small a number for valid comparison; herein the mortality was 66.6 per cent.

Of the total series of 264 cases, 56 (21 per cent) died in less than 48 hours, while 68 (26 per cent) died after this interval. The mortality of the total series was 47 per cent (124 patients). The treated and untreated groups had an identical 47 per cent mortality. Employing the aforestated criteria of Russek and Zohman as to the prognostic outlook during the first 24 hours of hospitalization, the total group can be divided as follows: 60 or 23 per cent "good risk," of whom 8 or 13 per cent received anticoagulants, and 204 or 77 per cent

TABLE II
Effect of Anticoagulants on Mortality Rate

Total days administered	Number of patients	Deaths	
		Pre-48 hr	Post-48 hr
Heparin alone			
1–2	3	2	0
3–4	1	0	1
5–7	2	0	1
More than 7	0	0	0
Unspecified	3	0	2
Totals	9		4
Dicumarol alone			
1–7	6	2	1
8–21	14	0	1
More than 21	1	0	0
Unspecified	9	0	3
Totals	30	2	5
Heparin and dicumarol			
Unspecified	27	2	6

TABLE III
Comparison of Mortality in Treated and Untreated Groups

Category	Total Cases		Treated		Untreated	
	Number	%	Number	%	Number	%
Deaths pre-48 hr	56	21.2	8	12.1	48	24.3
Deaths post-48 hr	68	25.8	23	34.9	45	22.7
Total deaths	124	47.0	31	47.0	93	47.0
Survivals	140	53.0	35	53.0	105	53.0
Totals	264		66		198	

"poor risk," of whom 58 or 28.4 per cent received this therapy. Table III relates the mortality before and after the first 48 hours of hospitalization to the treated and untreated groups. Death during the first two days is usually due to ventricular fibrillation, cardiac asystole, shock, or congestive heart failure—all unrelated to thromboembolic complications and therefore not preventable by anticoagulants.[35] Accordingly, the exclusion of patients dying in the first 48 hours of hospitalization reveals an over-all death rate of 32.7 per cent (reduced from 47 per cent), and death rates of 39.6 per cent and 30.0 per cent respectively for the treated and untreated groups. No important difference is noted between these groups whether the total mortality or post-48 hours mortality is considered.

TABLE IV

Mortality in Treated and Untreated Groups Related to Good Risk and Poor Risk Criteria

Category	Total cases		Treated		Untreated	
	Number	%	Number	%	Number	%
Good risk						
Deaths pre-48 hr	13	21.7	2	25	11	21.1
Deaths post-48 hr	7	11.6	3	37.5	4	7.7
Survivals	40	66.7	3	37.5	37	71.2
Totals	60	100.	8	100.	52	100.
Poor risk						
Deaths pre-48 hr	43	21.0	6	10.3	37	25.3
Deaths post-48 hr	61	30.0	20	34.5	41	28.1
Survivals	100	49.0	32	55.2	68	46.6
Totals	204	100.	58		146	

TABLE V

Comparison of Mortality of Treated and Untreated Groups after Elimination of Deaths in First 48 Hours

Category	Cases		Treated		Untreated	
	Number	%	Number	%	Number	%
Good risk						
Deaths post-48 hr	7	14.9	3	50.	4	9.8
Survivals	40	85.1	3	50.	37	90.2
Total	47	100.	6	100.	41	100.
Poor risk						
Deaths post-48 hr	61	37.5	20	38.5	41	39.6
Survivals	100	62.5	32	61.5	68	62.4
Total	161	100.	52	100.	109	100.

Table IV extends the previous tabulation further by relating time of death, treatment groups, and prognostic category. Although the number of "good risk" cases in each of the various subcategories is too small for valid appraisal, analysis of the "poor risk" group reveals no influence of the anticoagulants upon survival. Elimination of deaths in the first 48 hours reveals the similarity of results in treated and untreated, "good risk" and "poor risk" patients (Table V).

TABLE VI

Incidence of Hemorrhagic Complications

Hemorrhagic complication	Treated		Untreated	
	No. (66)	%	No. (198)	%
Major: hemopericardium (alone)	1	1.5	0	0
plus rupture of the myocardium	0	0	3	1.5
Minor: hematuria	4	6.1	2	1.0

Table VI summarizes the incidence of hemorrhagic complications, of which there were four major and six minor. Among those in the group treated with anticoagulants, there was one instance of hemopericardium without rupture of the myocardium and four of microscopic hematuria. No observations were made as to the incidence of thromboembolic complications in this study because of the lack of sufficient data for analysis.

Comments

As has been pointed out earlier, the anticoagulants cannot be expected to influence mortality in acute myocardial infarction during the first 48 hours. During this period, death is usually due to ventricular fibrillation, cardiac asystole, shock, or congestive heart failure—all of which are unrelated to thromboembolic complications. Wright,[25,28] on the other hand, is of the opinion that all cases of acute myocardial infarction should be placed on anticoagulant therapy as soon as the diagnosis is made. He believes that anticoagulants reduce the total mortality, and in addition, the occurrence of significant thromboembolic phenomena in survivors (e. g., hemiplegia).

In the 56 cases expiring in the first 48 hours, there was no important difference in survival between those receiving anticoagulants and those not receiving them, irrespective of the prognostic classification, i.e., "good risk" or "poor risk." However, it must be said that virtually all of the treated group did not attain satisfactory prolongation of the prothrombin or clotting times in the first two days, because some received dicumarol alone, whereas others received as little as one dose of heparin. This is a possible explanation for the ineffectiveness of the anticoagulants in our cases as measured by the pre-48 hour mortality.

In our series, there was no important difference in the mortality after 48 hours between those in the anticoagulant and those in the nonanticoagulant categories. We feel the ineffectiveness of the anticoagulants in our patients is even more meaningful when one considers that over twice as many "poor risk" cases (28 per cent) received the drugs as "good risk" cases (13 per cent). Any favorable influence of the anticlotting agents should be demonstrable in the "poor risk" group. How, then, does one reconcile these observations with the more favorable experience of Wright *et al.*[3,22–29] and even of Russek and his colleagues?[11–19] Could differences in the make-up of the various groups at least partially explain the discrepancies in end results? Table VII summarizes some of these basic differences. We feel these differences must be considered in comparisons of series of myocardial infarction when we are evaluating anticoagulants or any other modality of treatment. Zohman's composite series of 1,047 cases[30] comprised 623 from a municipal hospital, 223 from a voluntary institution, and 201 from a Marine hospital. Patients in the latter group were characterized as ". . .of excellent physical make-up and were accustomed to a strenuous type of existence." On the other hand, the patients from the voluntary hospital from the same series were described as ". . .a typically urban group, the majority of whom had led a more sedentary life."

TABLE VII

Differences in Case Material of Reported Series of Myocardial Infarction

Series	Total	Ward (%)	Private (%)	Municipal or county		Good risk (%)	Poor risk (%)
				Number	%		
Wright[29]	1,031	36.8	63.2	241	23.3	23	77
Zohman[30]	1,047	—	—	623	59.5	46.7	53.3
Present	264	100.	0	264	100.	22.7	77.3

The latter group, as compared to the former, had a greater average age and incidence of previous myocardial infarction and diabetes, all of which factors are known to influence the prognosis in this disease. In short, Zohman's series was composed of almost 60 per cent municipal hospital patients, while Wright's series had less than a quarter.

In their monograph,[29] Wright and his group recognize a difference between the private and ward patient with acute myocardial infarction. Thus, although the rate of thromboembolic complications did not differ significantly, i.e., 25.8 per cent vs. 26.4 per cent in the private and ward cases, respectively, among the control (untreated) group, and 10.0 per cent vs. 11.8 per cent in the private and ward cases, respectively, among the treated group, there was a statistically significant difference in the mortalities. Table VIII is taken from this study[29] by the American Heart Association. Wright states that ward cases are perhaps in poorer physical condition at the time of admission. Furthermore, the fact that 22 per cent of the private patients in his series had the services of a private-duty nurse as compared to 3 per cent of the ward groups, is noteworthy. By contrast, our series was made up exclusively of ward patients with a comparably small percentage of special nurses in attendance. For these reasons among others, the mortality rate in our series in both the patients receiving and those not receiving anticoagulants was much greater than in Wright's.

Although the percentage of "poor risk" cases in the American Heart Association study[29] is almost identical with that in ours, there is a great difference in mortality rates. Table IX relates our mortality rate to that of Wright and also to that of Russek and Zohman. As discussed elsewhere,[31] the high mortality rate in our series is attributed to the inclusion of more older patients and more critically ill patients, lack of private nursing care, and a significant incidence

TABLE VIII

Effect of Anticoagulants in Ward and Private Cases

Type of service	Wright's series[29]		Present series	
	Total cases	Mortality (%)	Total cases	Mortality (%)
Control				
Private (or semi-private)	155	19.8	—	—
Ward	281	25.2	198	47.0
Treated				
Private	221	11.4	—	—
Ward	343	11.4	66	47.0

NOTE: 31 cases receiving both ward and private care are omitted.

TABLE IX

Mortality in Poor Risk and Good Risk Group in Three Series of Cases

Series	Total	%	Deaths	%
Wright[29]	1,031	100.0	—	—
Good risk	179	17.0	3	1.7
Poor risk	852	83.0	187	22.8
Russek and Zohman[15]	1,047	100	—	—
Good risk	489	46.7	15	3.1
Poor risk	558	53.3	335	60.0
Present	264	100.0	—	—
Good risk	60	23.0	20	33.3
Poor risk	204	77.0	104	50.6

TABLE X

Mortality Rate in Treated and Untreated Cases. Comparison with Previously Reported Series (Adapted from Wright[29])

Series	Number of cases		Percentage dying	
	Control	Treated	Control	Treated
Wright	442	589	23.4	16.0
Feldman—Cook County, Chicago				
Including deaths within 48 hr	76	76	30.3	30.3
Excluding deaths within 48 hr	70	67	24.3	20.9
Mullins—Mercy, Pittsburgh	120	174	22.5	7.5
Zeluff & Field—Bellevue, New York				
Including deaths within 48 hr	100	80	40.0	25.0
Excluding deaths within 48 hr	83	70	27.7	14.3
22 Series (excluding pre-48 hr deaths in 2 & 4)	3,254	2,513	28.7	15.0
Present series				
Including deaths within 48 hr	198	66	47.0	47.0
Excluding deaths within 48 hr	150	58	30.0	39.6

of congestive heart failure, prolonged fever and tachycardia. Table X, adapted from the American Heart Association study,[29] illustrates graphically the wide range of mortality in acute myocardial infarction and its relation to the use of anticoagulants.

That the total mortality in our treated and untreated groups (47 per cent in each) was higher than the respective figures of 22 other series as reported in the aforementioned study, is noteworthy. Excluding deaths in the first 48 hours, this same difference applies to the mortality of our patients receiving anticoagulants. We believe these observations reflect the greater severity of illness in our cases, particularly of the treated group, as seen in a city

hospital population. In a critical paper published in the same year as the American Heart Association study, Evans[4] also presented a rather similar table of the differing mortality rates in this disease. In addition, he pointed out other variables, such as the incidence of thromboembolic complications, the role of intimal hemorrhage in the initiation of the disease, and the several stages of altered coagulability of the blood after the onset of the illness—any one of which may explain the discrepancies among series of cases treated with anticoagulants. Furthermore, there is doubt by some[32,33] that dicumarol acts as a satisfactory anticlotting agent *in vivo*, as well as *in vitro*, in the doses usually employed clinically. Wessler[33] demonstrated the ineffectiveness of this drug in the prevention of clotting in isolated segments of jugular and femoral veins of dogs. In a group of 18 animals given sufficient amounts of dicumarol to lower the 2-stage prothrombin concentration to a range of from 29 to 2 per cent of the control level, clotting *in vivo* in these isolated venous segments was not significantly retarded in 17. There was no serum prothrombin conversion accelerator activity in eight of twelve such animals tested.

If, however, one accepts the ineffectiveness of dicumarol as an anticlotting agent *in vivo*, one must explain the statistically significant reduction in mortality and morbidity in numerous studies usually attributed to this drug on some other basis.

The relation of hemorrhagic complications in acute myocardial infarction, both major and minor, to anticoagulant therapy is controversial. After a survey of the data of 228 physicians employing these agents, Russek and Zohman[21] recorded a range of 0.25 per cent major episodes with no deaths to 10 per cent major episodes with four fatalities from hemorrhage among 100 patients given dicumarol. Wright[29] reported an incidence of 12.9 per cent hemorrhagic episodes among the treated cases as against 5.2 per cent among the controls. He maintained, however, that in only 7.8 per cent of his treatment group were the bleeding episodes aggravated by the anticoagulants.

The three cases of cardiac rupture among our 198 untreated cases (1.5 per cent) and the absence of such episodes among our 66 treated cases contrast sharply with the experience of Wright.[29] The latter presented an incidence of 1.9 per cent and 3 per cent, respectively, while in the same year Waldron *et al.*[34] found 4.98 per cent and 14.1 per cent. On the other hand, Wright's figures for hemopericardium in the autopsy cases revealing no myocardial rupture are 2 per cent for the untreated and 12 per cent for the treated cases. Waldron's figures were 4.6 per cent and 10.7 per cent. In our series there was but one instance of hemopericardium without rupture of the myocardium; this occurred in a member of the anticoagulant group and amounted to 60 cc and was not believed to be a contributory cause of death.

Combining their cases of hemopericardium with and without myocardial rupture Wright and his colleagues[29] presented an incidence of 2.4 per cent in the controls and 4.1 per cent among the treated cases. The difference, or 1.7 per cent, is held to be the inherent risk of anticoagulants, and in their opinion is justified by the reduction of the mortality and of thromboembolic complications. By contrast, as has already been stated, in our series of 66 untreated

TABLE XI

Hemorrhagic Complications in Treated and Untreated Cases. Comparison with Previously Reported Series

	Treated (%)	Untreated (%)
Major		
Myocardial rupture plus hemopericardium		
Wright[29]	4.1	2.4
Present series	0	1.5
Hemopericardium alone		
Wright[29]	12	2.0
Present series	1.5	0
Minor		
Hematuria		
Wright[29]	6.6	1.4
Present series	6.1	1.0

patients, there were no deaths attributable to this therapy.*

The 6.1 per cent incidence of hematuria in our group treated with anticoagulants and the 1 per cent incidence in the group not treated with these drugs are almost identical with the figures of the American Heart Association study.[29] Table XI sums up our experience with hemorrhagic complications as compared with that of the latter report.

Summary

(1) The experience with anticoagulants in 66 patients as compared with 198 untreated during one year at a large municipal hospital has been presented.

(2) Anticoagulants did not improve the survival rate in this series.

(3) There was but one major hemorrhagic complication, i.e., hemopericardium without myocardial rupture, related to the use of these drugs, and this complication was not contributory to death. We observed three cases of cardiac rupture in patients who did not receive anticoagulants.

(4) The incidence of minor hemorrhagic complications, i.e., hematuria, in the treated group was of the same order as that previously reported by others.

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* In all this discussion it is assumed that the causes of death in nonautopsied fatal cases were proportionally similar to those of the autopsied cases.

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Experimental Studies

Cardiac Drug Responses and Potassium Shifts

Studies on the Interrelated Effects of Drugs on Coronary Flow, Heart Action and Cardiac Potassium Movement (Section I)

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THE SENSITIVITY of the myocardium to alterations in its electrolyte environment has been extensively studied. Danowski and Elkinton[7] in a detailed review on the effects of potassium on the functions of various organs and systems of the body, conclude that "the heart is the most sensitive of all organs to alterations in its extracellular potassium concentration."

It is now well established that the concentration of potassium in the extracellular fluid is low (4 to 5 meq per liter in plasma) while the intracellular concentration is considerably higher—approximately 40 meq per 100 grams of cat heart tissue.[34] While the exact role of this ion in cellular function is still obscure, there is no doubt that the maintenance of the intracellular-extracellular potassium relationship, within physiologic limits, is an indispensable condition for normal heart function.

In recent studies by Melville and Mazurkiewicz,[32] it was shown that the coronary flow and heart contraction (amplitude and rate) changes following injections of epinephrine or norepinephrine in the isolated heart were rather similar to those induced by perfusions with reduced potassium concentrations. During perfusion of the heart with decreasing potassium concentrations there was progressive augmentation of coronary flow associated with stimulated heart contractions. Ventricular irregularities and fibrillation also ensued rapidly with potassium-free perfusion. Moreover, as the concentration of potassium diminished, the sensitivity to epinephrine and norepinephrine was potentiated, and during perfusions with K-free Locke ventricular arrhythmias were readily precipitated by relatively minute doses (one microgram) of either agent. It was therefore postulated that the cardiac responses to epinephrine and norepinephrine might be partly or wholly mediated through loss of potassium from the heart. It was therefore of interest to investigate the general problem of the influence of drugs upon the heart under various conditions of potassium concentration in the perfusing fluid. Although it is well recognized that changes in electrolyte balance in the body can influence heart function, there are relatively few experimental studies in

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the literature on this question, with special reference to changes in the responses to drug administrations.

Historical

The effects of potassium on the cardiovascular system were studied as early as 1864 by Traube,[36] who reported that following intravenous injection of a toxic dose (250 mg) of potassium nitrate in dogs, there was a marked increase in blood pressure and slowing of the heart. Bunge[2] in 1871 confirmed these observations but concluded that the heart rate was altered only by toxic doses of potassium. Ringer[33] as early as 1883 concluded that an efficient perfusion fluid for the maintenance of normal heart activity must contain the proper proportions of sodium, calcium, and potassium salts and be slightly alkaline. Using potassium-free Ringer solution for perfusion of the isolated frog heart Gothlin[15] observed an increase in systolic contractions and a decrease in diastole, and concluded that these effects were due to an uncompensated calcium action and not to the direct removal of potassium *per se*.

Gross[16] first compared the actions of calcium and potassium on the isolated perfused heart and observed that following small doses of potassium chloride there was a decrease in the amplitude of contractions and in the heart rate, and diastolic arrest of the heart ensued after large doses. Conversely, following calcium chloride there was an increase in the amplitude of contractions and a slight increase in heart rate. These findings have been amply confirmed by numerous subsequent workers.

In 1911, Mathison[28] also compared effects of intravenous and intra-arterial injections of potassium salts. It was observed that intravenous injections in dogs caused a primary fall of blood pressure followed by a slight secondary rise, while intra-arterial injections (in the carotid artery) invariably caused a "large rise" of blood pressure. The close similarity between this latter effect and the response to injected epinephrine was also emphasized by this worker.

Using the isolated rabbit heart, McLean, Bay, and Hastings[30] reported that reduction of potassium in the perfusing fluid depressed the height of the T wave, while complete omission resulted in T wave inversion. Conversely, increasing the potassium content of the perfusion fluid to 9–18 mM/*l* prolonged the P-R interval and the QRS complex, indicating a depression of conduction. The sequence of electrocardiographic alterations associated with increased potassium in the perfusion fluid was first a prolongation of the P-R interval and then of the QRS complex—indicating again a slowing of conduction—and a pronounced increase in the height of the T wave. As the concentration of potassium was increased these changes were accentuated as seen by partial auriculo-ventricular block and ventricular tachycardia. At 18 mM/*l* potassium in the perfusion fluid, there was cardiac standstill.

Kehar and Hooker[22] showed that immediately following the initiation of electrical fibrillation in the dog heart, the perfusate showed an appreciable increase (from the control of 12.8 mg/100 ml to 15.0 mg/100 ml) in potassium. Associated with these changes there were profound histologic alterations in the heart tissue which had been fibrillating. These effects were also restored to normal by addition of potassium to the perfusing fluid.

Winkler, Hoff, and Smith[40] have also investigated the relationship between electrocardiographic alterations and changes in serum potassium concentration of dogs, following intravenous injections of potassium chloride. At serum potassium concentrations of 5–7 mM/*l*, T wave changes appeared regularly. When the serum potassium level was 8–10 mM/*l*, there was an associated depression of the S-T segment. Idioventricular block appeared at serum potassium concentrations of 10 mM/*l*, while the P waves disappeared when the serum potassium level ranged between 9–11 mM/*l*. Finally, cardiac arrest was evident when the serum potassium level was 14–16 mM/*l*. No ectopic arrhythmias of any type were observed in these experiments using slow rates of potassium infusion.

Butcher and associates[4] recorded action potentials simultaneously from the ventricular cavity and the epicardium of the ventricle of the isolated perfused heart, and observed that when the perfusing solution (Tyrode) contained more than 2.8 meq/*l* of potassium, the electrocardio-

grams showed prolongation of the QRS complex, shortening of the S-T interval, widening of the P waves and increased amplitude of the T wave. However, increasing the sodium of the perfusion fluid could partially reverse the changes observed with excess potassium. Complete absence of potassium from the perfusion fluid led to prolongation of the P-R interval, the QRS complex and the S-T interval and flattening of the T waves.

Using the cat papillary muscle Garb[14] studied the direct effects of various cations, recording both changes in the contractile force and in electrical potentials during fixed rates of stimulation and therefore without variations in either heart rate or rhythm or coronary blood flow. Doubling the potassium level to 11.3 meq/*l* resulted in depression of the T deflection and reduction of contractile force. It was also observed that associated with progressively increasing potassium concentrations, the T and the R deflections widened, the contractile force diminished and the T wave dipped further below the isoelectric line. When the potassium concentration was increased threefold, that is, to 16.9 meq/*l*, a single slow negative deflection was recorded, although no systolic contraction was produced. When the preparation was perfused with potassium-free Locke there was increased irritability of the muscle and a repetitive response (one to six times) to each applied electrical stimulus. At such a time, the pattern of the electrical response remained unchanged although all the potassium in the bath had been removed.

Magida and Roberts[26] studied the electrocardiographic changes following decreased plasma potassium, with and without concomitant alteration in plasma pH or bicarbonate content. The results showed a sequential lowering and inversion of the T wave which occurred simultaneously with the fall in plasma potassium concentration. However, if the plasma pH and bicarbonate were maintained at normal levels, these changes were minimal.

In the advanced stages of excessive serum potassium elevation in man, Lenzi and Canniggia[23] have summarized the main electrocardiographic modifications as follows: (1) Shortening of the Q-T complex—this shortening is often more relative than absolute and is only valid if correlated with the heart rate; (2) prolongation of the time of depolarization (QRS complex); and (3) changes in the S-T interval and the T wave which have been subdivided into three different phases. Thus, in the *first* phase, the T wave is positive and peaked; in the *second* phase, the S-T interval declines below the isoelectric line, and the T wave becomes biphasic beginning negatively; and finally, in the *third* phase, the T wave is absorbed completely. Levine[24] has also summarized the main electrocardiographic changes associated with potassium imbalance in man.

More recently, Grumbach, Howard and Merrill[17] have reinvestigated the relationship between calcium and potassium ions and the initiation of ventricular fibrillation in the isolated rabbit heart, perfused with a normal Krebs-Henseleit solution or Krebs-Henseleit solution modified in respect to potassium and calcium content. Electrical activity was determined from electrograms recorded directly from the heart. In these experiments, it was found that fibrillation was initiated by the perfusion of potassium-free solutions *only when the calcium content is present in a concentration of 3.5* meq/*l or greater*. Moreover, fibrillation could not be initiated by steady state perfusion with high calcium solutions, if the potassium concentrations of the perfusion medium is 2.3 meq/*l* or greater. These authors also showed that fibrillation could be induced *immediately* following rapid injections of hypertonic calcium chloride solutions, when the potassium concentration of the perfusion solution is greater than 2.3 meq/*l*. It was therefore concluded that calcium chloride fibrillation depended upon sufficiently rapid elevation of the absolute calcium concentration in the tissue fluid to a critical level, and that ventricular fibrillation followed potassium-free perfusions, because of failure of the heart to resist the stimulating action of the relatively increased calcium present in the perfusing solution.

Harris[18] has reported that the initiation of ectopic beats from the dog's heart following infarction, induced by ligation of the anterior descending coronary artery, is due to changes in potassium. Potassium concentrations in the coronary blood venous samples draining ischemic

areas were found to be about double that of the control samples. It was also reported that the injections of potassium chloride into the coronary arteries of normal dogs produced ventricular ectopic beats, ventricular tachycardia, and ventricular fibrillation. In view of these findings, it was concluded that the increased release of potassium in the infarcted myocardium is an important excitatory factor in myocardial ischemia.

In regard to the effects of autonomic drugs on blood potassium levels, D'Silva,[8–12] Brewer, Larson and Schroeder[1] and Martin,[27] have all reported that following injection of epinephrine and related sympathomimetic amines, there is a transitory increase in serum potassium concentration in laboratory animals. This effect, however, appeared to be due to changes in the liver, rather than to the associated cardiovascular effects, since it was abolished by hepatectomy.

Robertson and Peyser[34] have reported that following rapid excision of the heart, the total cardiac muscle potassium, as determined shortly (1 to 12 minutes) following injection of 500 μg of epinephrine or norepinephrine in anesthetized cats, was significantly decreased. However, smaller doses of the amines were without effect.

On the other hand, Mathison,[28] McGuigan and Higgins[29] and Camp and Higgins[5] have emphasized the similarity between the cardiovascular and other actions of epinephrine and the effects of injections of potassium in experimental animals. Indeed, the latter authors concluded: "The effects produced by epinephrine and the potassium ion are the same and since epinephrine causes a passage of potassium from the tissue, we believe that the changes effected by epinephrine are in fact produced by potassium migration." Nevertheless, Martin[27] suggested that since the increase in serum potassium following injection of epinephrine in the cat is slower and more prolonged than the blood pressure change, the latter cannot be due to the former.

The effects of acetylcholine on the heart function with special reference to changes in potassium and calcium concentrations were first studied by Clark[6] on the isolated frog heart. It was reported that as the concentration of potassium in the perfusing fluid increased above the normal, the isometric response is reduced, while decreasing the potassium concentration below normal increased this response. In addition, it was noted that reduction of potassium concentration increased the sensitivity of the heart to acetylcholine, while conversely, increasing the potassium concentration decreased sensitivity. When the calcium content of the perfusing fluid was increased, the response to acetylcholine was also diminished but reduction of calcium below normal did not appear to influence the sensitivity of the response to acetylcholine. It is now well known that acetylcholine can induce characteristic cardiac arrhythmias and electrocardiographic changes—partial or complete heart block, diphasic and notched P waves, decreased amplitude of the P waves, atrial tachycardia, as well as fibrillation and various degrees of ventricular depression including cardiac standstill. Moreover, after previous atropinization of the isolated mammalian heart, injection of acetylcholine can induce cardiac stimulation. This effect is due to liberation of some adrenaline-like substances,[21] and under such conditions acetylcholine can also be shown to induce ventricular arrhythmias.

More recently, employing intracellular microelectrodes, Hoffman and Suckling[20] have studied the effects of changes in the extracellular concentrations of calcium and potassium on the transmembrane resting and action potentials of single fibers of the auricle, ventricle, and specialized conducting system of the dog heart. They observed that changes in calcium concentration alter the time course of the action potential recorded from auricle and ventricle, but had little effect on the action potential of the Purkinje fibers. The authors conclude that the effects of potassium on the resting transmembrane potential are dependent on the simultaneous calcium concentrations. However, Weidmann[37] earlier showed that in the isolated Purkinje fiber changes in calcium concentrations, ranging from 10.8 to 0.68 mM/*l*, led to little or no change in either the size or shape of the action potential and the magnitude of either the resting potential or the transmembrane resistance. Burgen and Terroux[3] have also concluded from studies of the isolated cat auricle that increase in extracellular potassium concentration leads to a

progressive decrease in resting transmembrane potential, and under the influence of acetylcholine or carbamylcholine, the resting potential was increased; the action potential decreased in duration (as a result of the increased rate of repolarization) and the active membrane potential was unchanged. The problem of the relationship of ionic changes to the electrical phenomena observed with the use of intracellular recordings from the heart has been reviewed by Weidmann.[38] It must be concluded, however, that the role of calcium and/or potassium in the regulation of membrane activity and permeability is still rather obscure.

Methods

Isolated rabbit hearts perfused by the modified Langendorff procedure of Lu and Melville[25] and Melville and Mazurkiewicz,[32] were used in all experiments. The rabbit was killed acutely by a blow on the head. Immediately thereafter the thorax was opened and the heart removed and placed in Locke's solution at room temperature. The aorta was then tied to the tip of the perfusing cannula, and any extraneous tissues removed. The whole perfusion apparatus was previously completely filled with warm oxygenated solution. The recording lever ("Fixit") was attached close to the apex of the left ventricle by a fine sterling silver wire, which also served as one of the leads for the electrical recordings and which will be described in more detail later. The setting up of the heart took between two and three minutes to perform.

Perfusion Fluid: In order to ensure stabilization of the preparation, the heart was maintained at the beginning of all experiments with normal Locke's solution for 15 minutes prior to any treatment. When necessary, the heart was maintained for a further 15 minutes with the "modified Locke solution" under study before the drug effects were investigated. However, when the heart was being perfused with Locke's solution completely lacking in potassium, normal heart activity could only be temporarily maintained by repeated injections of potassium chloride (25 mg) from time to time, as will be indicated.

Since the potassium or calcium content of the Locke's solution employed was altered in different experiments, it should be stated that "normal Locke's solution" as referred to throughout, consisted of: NaCl, 0.92 per cent; KCl, 0.042 per cent; $CaCl_2$, 0.024 per cent; $NaHCO_3$, 0.015 per cent; and glucose, 0.1 per cent. The ionic concentrations were Na^+, 158 meq/*l*; K^+, 5.6 meq/*l*; and Ca^{++}, 4.2 meq/*l*. All solutions were freely oxygenated throughout the experiments.

When modified Locke's solutions were employed no attempt was made to maintain isotonicity. It has been reported by Butcher and associates[4] that addition or subtraction from the standard perfusion fluid of 34 meq/*l* of sodium and chloride had little or no effect on the electrocardiograms recorded from the isolated rabbit, dog, or turtle hearts. Since the osmotic changes produced by altering the concentration of potassium during the experiments reported here were maximally of the order of 5.6 meq/*l*, failure to balance to isotonicity should not alter significantly cardiac function. However, in some experiments, where isotonicity was restored by adding the calculated equivalent amounts of sodium chloride, similar results to those described were also obtained.

Electrograms: Electrograms were recorded on a Sanborn Viso-Cardiette using the standard lead II position, attaching the leads to two sterling silver wire (0.01 inch diameter) electrodes connected with the heart. In all experiments, the right arm lead was connected to one wire tied around the aortic stump over the thread attaching the aorta to the perfusion cannula. The left leg lead was connected to another similar wire which was passed with a curved needle through the myocardium at the apex of the ventricles. This also served to tie the heart to the recording lever, and in this way the electrode was securely fixed. Care was taken to avoid contact of the electrode through the perfusing liquid with the metal of the recording lever in order to prevent short-circuiting. This was accomplished by covering the electrode at the apex of the ventricle as completely as possible with plasticine. In Figure 1 the orientation of the heart and the disposition of the electrodes are shown diagrammatically. This arrangement was uniformly employed throughout in order to obtain as far as possible constant and repeatable control electrical patterns.

Potassium Determinations: Potassium determinations were made by standard flame photometric procedures. Samples of the perfusate were collected for short (5 to 30 sec) intervals immediately before, and at varying times after the injections. Samples of the perfusing fluid were collected from a side arm in the system, close to the attachment of the perfusion cannula both at the beginning and at the end of each experiment. To 1 cc of each sample was added 1.73 meq sodium, in the form of sodium chloride, and diluted up to 50 cc with distilled water. The excess of sodium was added in order to eliminate interference due to otherwise unknown variations in the sodium content of the different samples. Standard solutions with final potassium concentrations ranging from 0.1 to 20 parts per million (p.p.m.) were made as necessary.

The potassium determinations were made with a Beckman D.U. Spectrophotometer with flame attachment using a wave length of 768 mμ, slit width of 0.3 mm, and one-half sensitivity. The oxygen-acetylene pressure ratio was 10:2. In order to ensure a stable flame emission a reading of a standard solution containing a potassium concentration close to the unknown sample was made prior to each sample evaluation. All analyses were done in duplicate and varied less than 3 per cent.

The concentration of potassium in the unknown samples was obtained from the curve of the standard potassium solutions expressed as parts per million on the abscissa and optical density as read on the ordinate.

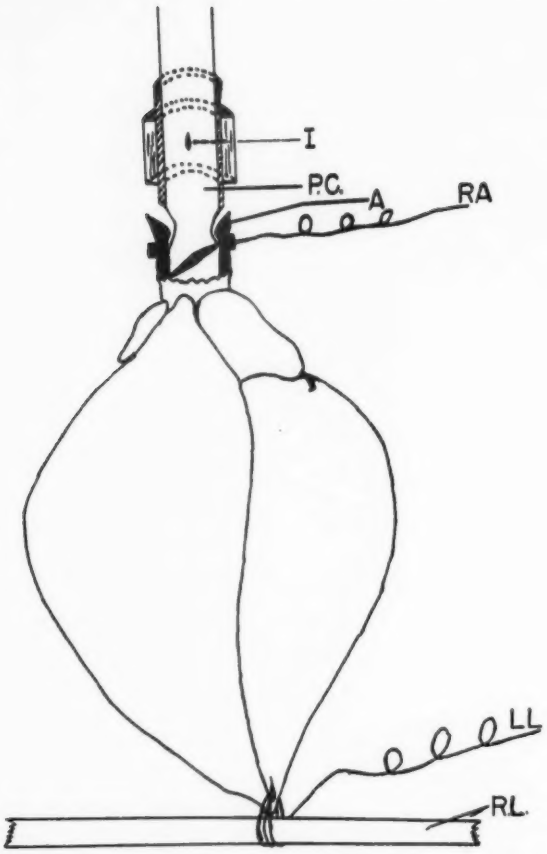

Fig. 1. Orientation of the electrodes on heart. I—site of drug injection; P.C.—perfusion cannula; A—aorta; RA and LL—right arm and left leg lead connections for recording (see text); and R.L.—contraction recording lever.

The values obtained were converted from parts per" million" as measured from the standard curves by multiplying by the dilution factor (50 times) and then dividing by the molecular weight of potassium (39.1). These calculations give measurements in units of meq/*l* of potassium in the original solutions.

Potassium Shift: The "*net gain*" or "*net loss*" of potassium from the heart was calculated as the difference between the amount of potassium *entering* and that *leaving* the heart during a given 10 second period. This was the average time for collections of adequate samples of the perfusates. Corrections for variations in rates of coronary flow were made by multiplying the potassium concentration (milliequivalents per liter) of the sample by the associated coronary flow rate (cc per 10 sec), as calculated from the records obtained at the time the sample was collected. Consequently, the amount of potassium entering or leaving the heart is expressed as *microequivalents per 10 seconds* (μeq/10 sec).

In some experiments, radioactive K^{42} was used for determining the exchange rate of potassium in the isolated perfused rabbit heart. Trace amounts of K^{42} (K_2CO_3) were added to the main reservoir containing the perfusion fluid and thereby distributed to all parts of the perfusion system. In all such experiments, the final concentration of K^{42} in the perfusion fluid was at least 100 times over background. Samples (marked S on the records) of the perfusate were collected for short (5 to 30 seconds) intervals of time, *immediately before* and at varying times during the period of action of the agent. Samples of the perfusion fluid were collected from a side arm in the system close to the perfusion cannula at varying times, just prior to injecting the drug and at the end of the drug response, after the last perfusate sample was obtained.

The amount of radioactive K^{42} in each sample was measured on a Berkeley Decimal Scaler, Model 2105, with a thin end window Geiger-Müeller tube. The sample plates were prepared by pipetting 0.5 cc of the sample on aluminium discs. After the discs were dried under a heat lamp they were placed into the counting chamber of the lead castle and the time taken to make a pre-determined number of counts was recorded. Necessary corrections were made for decay of the radioactive K^{42} (half-life of 12.4 hours), background, and to correct the sample to one ml volume.

Potassium Exchange: The rate of exchange of radioactive potassium was calculated from the difference between the amount of K^{42} (in counts per minute per cc) *entering*, and the amount of K^{42} (in counts per minute per cc) *leaving*, the heart during a given 10 second period. Again, variations in coronary flow at the time each sample was collected were corrected for by expressing the amount of K^{42} entering or leaving the heart as a product of the K^{42} concentration (counts per minute per cc) and the coronary inflow (cc per 10 seconds) at the time the sample was collected. The rate of exchange of potassium is expressed in minutes^{-1} and was obtained by using the rate constant formula:

$$K^{42} \text{ exchange equals } \frac{0.693}{t^{1/2}}$$

where $t^{1/2}$ is the time required for 50 per cent exchange.

The influence of the different agents upon inward exchange rate of K^{42} was obtained by administering the drugs approximately 15 min after the exposure of the heart to the radioactive potassium Locke's solution was started. The influence of the drug treatment on the outward exchange rate of K^{42} was obtained, after the heart had been previously maintained on a radioactive K^{42} Locke's solution for 30 min (in order to permit almost complete saturation); whereupon the perfusion fluid was changed to normal (nonradioactive potassium) Locke's solution, and after a ten min period in all cases, the drug under investigation was injected. Samples of the perfusion fluid and of the perfusate were then collected and the counts/min determined, as described above. After the radioactive potassium in the samples was allowed to decay sufficiently (about one week), determination of "*net gain*" or "*net loss*" of potassium (K^{39}) were also made on these samples.

Drugs Tested: A total of 243 experiments were per-

formed in this study. Six experiments were done with each agent during perfusion of the heart with each of the different perfusion fluids. Triplicate experiments were done with each drug when the exchange rate of potassium (K^{42}) was studied.

Freshly prepared solutions of all drugs were employed, and a volume of 1 ml injected in each case. To avoid deterioration of the sympathomimetic amines during the course of lengthy experiments, the solutions were kept on ice throughout the experimental period, and the final dilution made with warm solution just prior to injection. All injections were made close to the heart through a short piece of rubber tubing connecting the perfusing cannula with the apparatus.

The drugs which were investigated and the doses which were selected for comparative studies were as follows:—*l-epinephrine bitartrate** (referred to throughout as epinephrine or by the abbreviation ADR), 100 μg; *l-norepinephrine bitartrate** (referred to throughout as norepinephrine or by the abbreviation NAD), 100 μg; *isoproterenol hydrochloride** (referred to as isoproterenol or by the abbreviation IS), 1 μg; *aminophylline* (abbreviated–AP), 5 mg; *acetylcholine chloride* (abbreviated AC), 100 μg; and *nitroglycerin* (abbreviated NG), 1 mg. In a number of other experiments, smaller or larger doses of these agents were employed but the results obtained were in general rather similar. However, as no complete comparative dose-response studies were performed these latter data are not included.

Results

1. Observations on the effects of various cardiac stimulants on coronary flow, heart action, and associated potassium movement in the heart

In the experiments presented in this section, the effects of epinephrine, norepinephrine, isoproterenol, and aminophylline are described. The changes induced by each agent were investigated during perfusion of the heart with either (a) normal Locke's solution, or (b) Locke's solution containing reduced potassium concentrations (50 to 25 per cent of normal potassium content), or (c) potassium-free Locke's solution.

Normal Locke's Solution: In general, concomitant with the cardiac stimulation induced by each of these agents, there was an associated coronary dilatation with an increased "net loss" of potassium from the heart. Figure 2 shows a typical example of these responses, as observed following an injection of 100 μg of epinephrine (ADR) while the heart was being perfused with normal Locke.

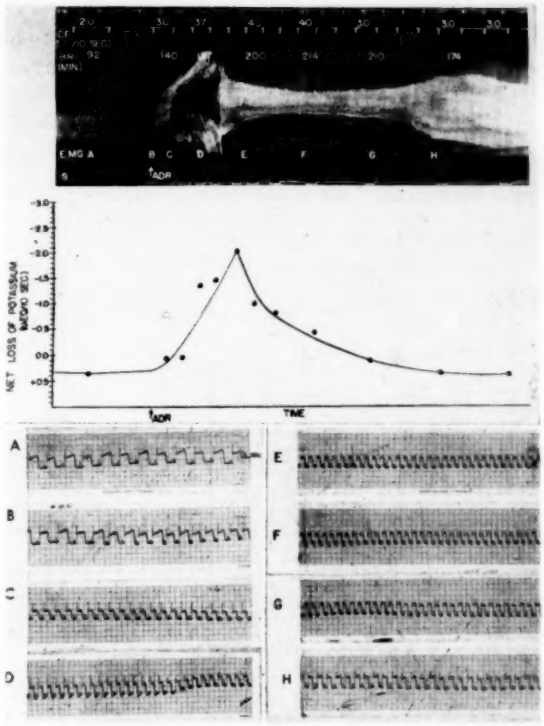

Fig. 2. Isolated rabbit heart perfused with normal Locke's solution. In all of the succeeding figures, the records are similarly arranged as follows: *Upper Record:* T, time in intervals of 10 sec; C.F., coronary inflow in cc/10 sec. Each mark on the line corresponds to the passage of the "indicator" in front of each photoelectric cell, alternatively; and, each interval represents an inflow of 3.55 cc. H.R., heart rate/min, as calculated from the record of the heart contractions (systole upwards, diastole downwards) as shown; EMG, electrograms taken at A to H; on the lower line, S, the times of drug injection and of collections of perfusates leaving the heart, are shown. *Middle Graph:* Time (abscissa) is on the same scale as the kymograph record above. Graph showing calculated net gain (+) or net loss (−) of potassium expressed as μeq/10 sec (ordinate). (See methods). *Lower Record:* Associated electrograms taken at A to H, as marked on kymograph tracing above. At arrow, ADR, 100 μg of epinephrine was injected.

As can be seen from the kymographic record (Fig. 2, upper tracing), almost immediately following the epinephrine there was an intense stimulation of both the amplitude and rate of the heart contractions, associated with a two-fold increase in coronary flow. These changes were fairly well sustained for the duration of the record (approximately 3 minutes). It is clear that during the initial intense cardiac stimulation, there is a significant "net loss" of potassium—from a control slight "net gain" of 0.35 μeq per 10 seconds to a maxi-

* Kindly supplied by the Sterling-Winthrop Research Institute, Rensselaer, New York.

TABLE I

The Effects of Epinephrine, Norepinephrine, Isoproterenol, and Aminophylline on Coronary Flow, Heart Contractions, and Potassium Shift, during Perfusion with Normal Locke's Solution or Locke's Solution Containing 25% of Normal Potassium

Agent and dose	No. of experiments	Contraction amplitude mean change %	Heart rate mean change (%)	Coronary flow mean change (%)	Potassium shift mean change μeq/10 sec	Perfusing fluid employed
Epinephrine 100 μg	12	105 (40–135)†	115 (85–130)	66 (31–100)	−2.29 (−1.48 to −2.66)	Locke
Norepinephrine 100 μg	11	100 (70–135)	140 (80–200)	100 (50–130)	−2.30 (−1.60 to −2.55)	Locke
Isoproterenol 1 μg	6	85 (60–180)	160 (60–210)	140 (60–300)	−2.06 (−1.87 to −2.62)	Locke
Aminophylline 5 mg	6	130 (80–195)	85 (45–115)	90 (70–125)	−1.87 (−1.42 to −2.10)	Locke
Epinephrine 100 μg	9	117 (62–188)	124 (70–160)	95 (60–149)	−2.34 (−1.00 to −2.77)	25% K Locke
Norepinephrine 100 μg	10	120 (65–180)	190 (130–220)	80 (30–140)	−2.25 (−1.70 to −2.48)	25% K Locke
Isoproterenol 1 μg	6	115 (75–190)	145 (100–250)	100 (70–220)	−2.32 (−1.91 to −2.51)	25% K Locke
Aminophylline 5 mg	7	115 (60–190)	95 (55–170)	95 (50–165)	−1.86 (−1.10 to −2.42)	25% K Locke

* See text.

† Figures in parentheses give ranges of maximal changes during the post-injection periods, as compared with the control periods. (−) = "net loss."

mum "net loss" of 2.00 μeq per 10 sec. It is to be noted that the shift in potassium gradually returns towards the normal preinjection level, although stimulated heart action was still apparent.

The lower section of Figure 2 shows representative samples of the associated electrograms taken at A to H. Thus at A, during the preinjection period, there is an initial sharp positive P deflection, followed by a high spiked R and sustained positive S-T segment. These deflections are of considerably higher voltages than are observed in the normal electrocardiogram, as is evident from the standardization (1 mv corresponds to a deflection of 3 mm). The records from B to H show that during the post-epinephrine period, there was progressive tachycardia, reaching a maximum of 214 beats per min (F), from the control rate of 92 beats per min (A). The form of the electrograms was not significantly altered and there was no evidence of any arrhythmias.

Similar results to those described above were obtained in 12 experiments, the data from which are summarized in Table I. The table shows comparatively the mean maximal changes observed in contraction amplitude, coronary flow, and potassium shifts following injections of epinephrine (ADR), norepinephrine (NAD), isoproterenol (IS), and aminophylline (AP), during perfusions with either normal Locke's solution, or Locke's solution with decreased potassium (25 per cent of the normal K^+).

Although the data show that rather similar qualitative changes were induced throughout by each agent, there are some quantitative differences which should be noted. Thus, the mean increase in contraction amplitude was most marked with aminophylline while both mean increases in heart rate and in coronary flow were most intense with isoproterenol. On the other hand, the greatest mean "net loss" of potassium was recorded in the epinephrine and norepinephrine experiments. It would rather appear from these findings that the observed potassium shifts do not depend entirely upon either amplitude or heart rate changes. More will be said about this later.

Locke's Solution With Reduced Potassium: In other experiments in which the potassium con-

centration was reduced to one-half of the normal (2.8 meq/*l*) relatively normal heart action could be maintained for several hours, and under such conditions the responses to the various agents were not significantly different from those observed with normal Locke's solution.

When the concentration of potassium in the perfusing fluid was reduced to 25 per cent of the normal (1.4 meq/*l*), again relatively normal heart activity (mechanical and electrical) could be maintained for periods of 30 to 60 min, and often longer. However, with prolonged perfusion progressive deterioration of heart function and occasional ventricular ectopic beats often ensued. In each of the experiments in this group, the drug was injected following an initial 15 min of perfusion with the altered Locke's, and in many instances a second injection was made 15 to 20 min later, that is 30 to 40 min after the perfusion was started.

In Table I are also summarized data from nine such experiments with epinephrine, ten with norepinephrine, six with isoproterenol, and six with aminophylline. In general, the cardiac stimulation and coronary dilatation observed under the conditions were more marked than during perfusion with normal Locke's solution, although the mean potassium shifts were not significantly different. In Figure 3 are shown typical examples of these responses, as were observed following injections of epinephrine.

As can be seen from the upper record following the injection (ADR) there was a prompt marked increase in rate and amplitude of contractions associated with increased coronary inflow (from 2.1 cc per 10 sec to 4.4 cc per 10 sec within 40 sec after the injection). Both the increased coronary flow and the cardiac stimulation diminished progressively, but were still in evidence 4 min after the injection.

The middle graph shows the "potassium shift," and as can be readily seen, again there is a marked "net loss" of potassium (from the control of 0.67 μeq per 10 sec to 2.13 μeq per 10 sec). This effect was not sustained, despite the continued evidence of cardiac stimulation.

In regard to the electrograms (lower section, Fig. 3), during the control period (A), the heart rate was rather slow (57 per min), but the characteristic P deflections followed by high positive R waves can be seen. During the control period in this experiment, there was also a less sustained S-T segment than usual, and definite inversion of T wave below the isoelectric line. Following the injection there was an immediate increase in heart rate to 174 per min (B) associated with no significant change in the P and S complexes, but diminution in the negativity of the T wave. Records C, D, and E show progressive sinus tachycardia, reaching a maximum of 195 beats per min in E. There was no evidence of any arrhythmias in either C or D; but at E, there was impaired intraventricular conduction, as shown by the prolongation of the QRS complex, and an elevated and

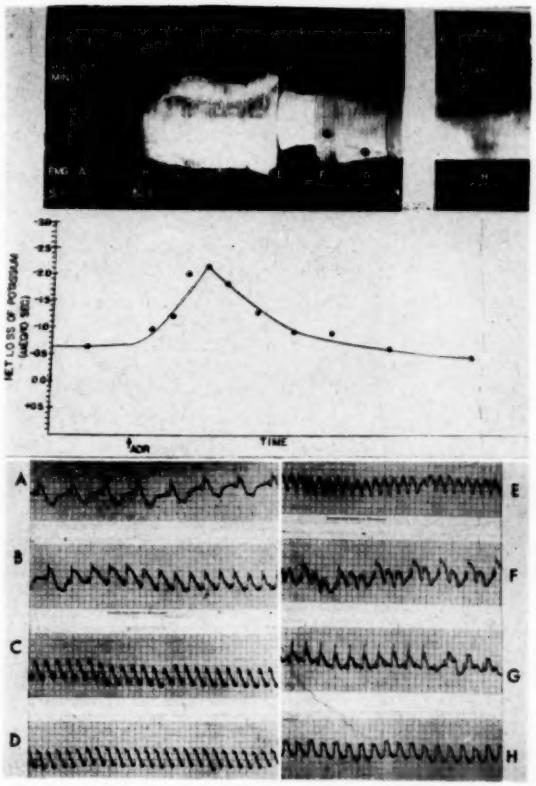

Fig. 3. Isolated rabbit heart perfused with Locke's solution containing 25 per cent (1.4 meq/*l*) of the normal potassium. (See legend, Fig. 2.) At arrow, ADR, 100 μg of epinephrine was injected, 15 min after start of perfusion.

more sustained S-T segment can be noted. Records F and G show clearly transient "coupled beats" from two different foci, and at G, there was a continuation of the multifocal rhythm with periods of 2:1 auriculoventricular block. Although the tachycardia persisted, relative restoration of the normal pattern of electrical activity is shown at H. The changes which were observed in corresponding experiments with norepinephrine were rather similar, and need no further comment.

With the other two agents (isoproterenol and aminophylline) the changes observed with the initial injections of both were also rather similar to those following epinephrine and norepineph-

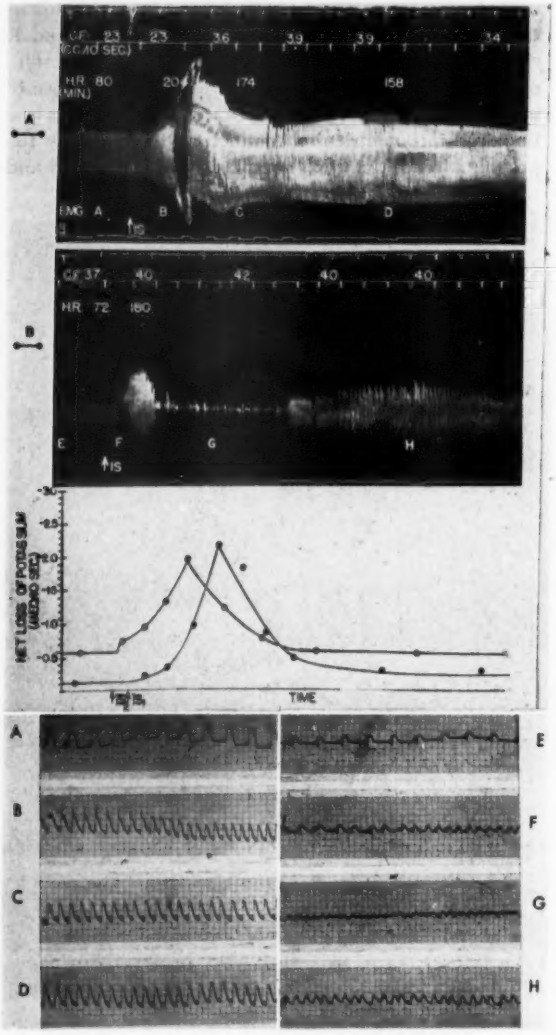

Fig. 4. Isolated rabbit heart perfused with Locke's solution containing 25 per cent of the normal potassium. (See legend, Fig. 2.) *Upper Kymograph Record:* At arrow, IS, 1 μg of isoproterenol injected after 15 min perfusion. *Lower Kymograph Record:* At arrow, IS, 1 μg of isoproterenol injected 40 min after perfusion began. *Middle Graphs:* Calculated "potassium shifts" associated with the above responses. *Lower Record:* Associated electrograms taken at A to H, as marked on kymograph tracing above.

rine, but when the perfusions with Locke containing 25 per cent of the normal potassium was continued for some time, repetition of the injections led to marked ventricular arrhythmias. Some examples of these are shown in Figures 4 and 5.

As can be seen from the upper kymograph record (Fig. 4) following the first injection of isoproterenol, there was the usual sustained increased coronary flow, associated with intense and prolonged cardiac stimulation and acceleration. However, the lower kymograph record shows that with prolonged perfusion, the increased coronary flow persisted, but the heart contractions were weaker and slower. Following a second injection (IS, lower record) there was only a brief initial tachycardia (180 per min), followed by a longer period of irregularities, which continued for 3 to 4 min. Following each injection of isoproterenol there was also a striking "net loss" of potassium as shown graphically (middle graphs).

The electrograms show that during the control period,

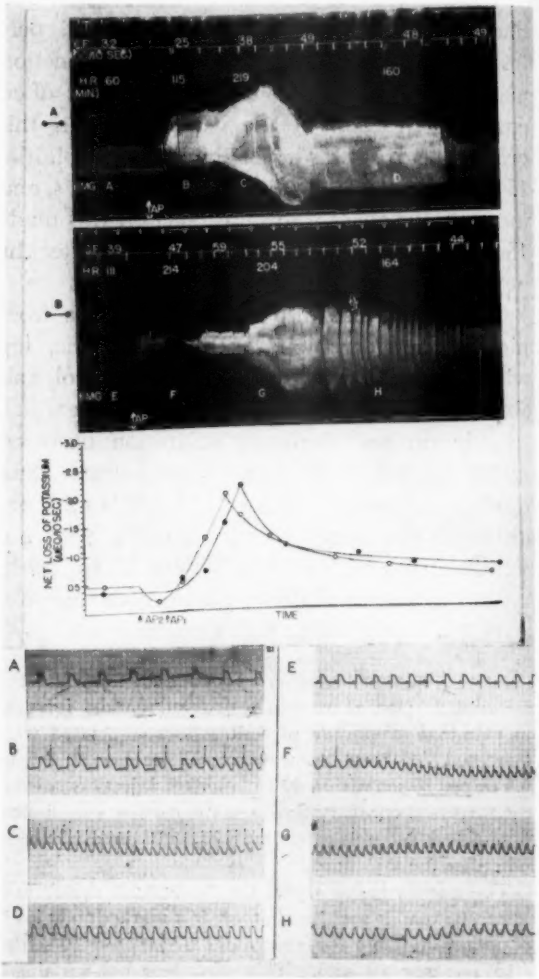

Fig. 5. Isolated rabbit heart perfused with Locke's solution containing 25 per cent of the normal potassium. (See legend, Fig. 2.) *Upper Kymograph Record:* At arrow, AP, 5 mg of aminophylline injected after 15 min perfusion. *Lower Kymograph Record:* At arrow, AP, 5 mg of aminophylline injected 45 min after perfusion began. *Middle Graphs:* Calculated "potassium shifts" associated with each of the above responses. *Lower Record:* Associated electrograms taken at A to H, as marked on kymograph tracings above.

despite the reduced potassium, the electrical pattern of the heart differed little from that observed during perfusion with normal Locke's solution. However, following the first injection of isoproterenol, there was a prompt and sustained tachycardia (B, C and D); record B shows a transient period of shift in the P wave, probably of nodal origin. With continued perfusion of the heart, the rate again slowed, and while the form of the electrogram returned to the normal pattern, all complexes showed lower voltages (E). At this time, repetition of the isoproterenol precipitated multifocal ventricular beats (F) followed by transient ventricular fibrillation with discernible auricular beats (G), and later A-V dissociation (H).

Similarly, in Figure 5 are shown the effects of repeated injections of aminophylline, during prolonged perfusion with 25 per cent K^+ Locke's solution. As can be seen following the initial injection (upper kymograph tracing), there is marked cardiac stimulation and coronary dilatation. However, repetition of the injection later (lower kymograph tracing) led to a prompt and more intense cardiac acceleration, with sustained systolic contracture followed by prolonged stimulation with gross irregularities. Following each injection there was again an increased "net loss" of potassium (middle graphs).

The associated electrograms show that following the first injection of aminophylline, there was also a run of coupled ectopic beats (B), which was followed by auricular paroxysmal tachycardia (C) and restoration to the normal type of QRS complexes. At D, the tachycardia still persisted. Prior to the second injection of aminophylline, as shown at E, there was a return to more or less normal contour, but the rate was still high. However, within 30 sec after the injection a nodal tachycardia ensued (F and G), with some tendency towards restoration to normal rhythm with A-V dissociation at H.

Potassium-Free Locke's Solution: During perfusion of the heart with potassium-free Locke's solution, there was always a rapidly progressive increase in the amplitude of the contractions and increased coronary flow, followed by tachycardia with ventricular ectopic beats; and, with continued perfusion ventricular fibrillation invariably occurred within 10 to 15 minutes. However, in such experiments relatively normal heart action could be restored temporarily for short intervals by injections of high doses of potassium chloride. In Figure 6 are shown results of a typical experiment of this type.

As can be seen in Figure 6, when the perfusing fluid is changed from normal Locke's solution (A) to potassium-free Locke's (K-free) with continued (3 min) perfusion there is a marked augmentation of the amplitude of the heart contractions, associated with definite increased coronary flow (B). The associated electrograms also show the normal control pattern (A), followed by definite prolongation of the QRS complex and marked sagging of the S-T segment (B), although the heart rate was not significantly changed. On further perfusion for 3 min, as marked at C (upper tracing), an electrogram showed the characteristic pattern of ventricular fibrillation, although as can be seen the auricular rate and pattern remained normal. At D, one minute later, ventricular fibrillation is still in evidence but there is also discernible irregular auricular activity.

When a large dose (25 mg) of potassium (KCl) is injected as shown at E, there is immediate brief (20 sec) disappearance of both mechanical and electrical activity, followed by subsequent restoration of relatively normal heart activity for some time. These changes are strikingly seen from the electrograms marked E, F, G, and H. Finally, the more or less complete restoration of normal electrical activity in the heart is seen by comparing the electrograms H and A.

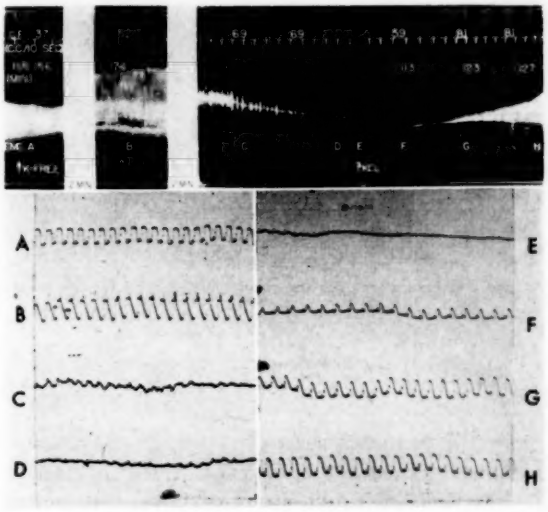

Fig. 6. Isolated rabbit heart, perfused with potassium-free Locke's solution. (See legend, Fig. 2.) *Upper Record:* At arrow (K-free) perfusion changed to potassium-free Locke's solution. At arrow, KCl, 25 mg of potassium chloride injected. *Lower Record:* Associated electrograms taken at A to H as marked on kymograph record above.

In Figure 7 are shown results of a typical experiment, in which the heart was continuously perfused with potassium-free Locke's solution, but prior to the start of the upper record (2 min earlier) a large dose (25 mg) of potassium chloride was injected. As can be seen, (upper kymographic tracing) normal heart contractions were temporarily restored, and injection of 100 μg of epinephrine (ADR) induced intense cardiac stimulation associated with increased coronary flow. These responses were also quite prolonged. The associated electrograms (A to E) were also rather similar to those obtained during perfusion of the heart with normal

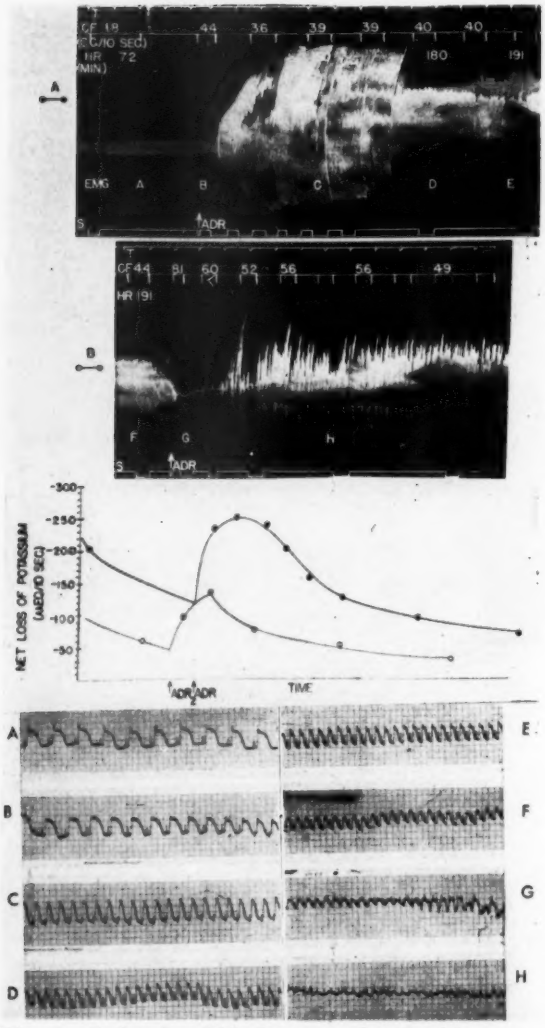

Fig. 7. Isolated rabbit heart perfused with potassium-free Locke's solution. (See legend, Fig. 2.) *Upper* and *Lower Kymograph Records* are continuous. The upper tracing was started 2 min after an injection of 25 mg of KCl (as in Figure 6). At each arrow marked ADR100 μg of epinephrine was injected. *Middle Graphs:* Calculated "potassium shifts" associated with each response. *Lower Record:* Associated electrograms A to H, as marked on kymograph tracings above.

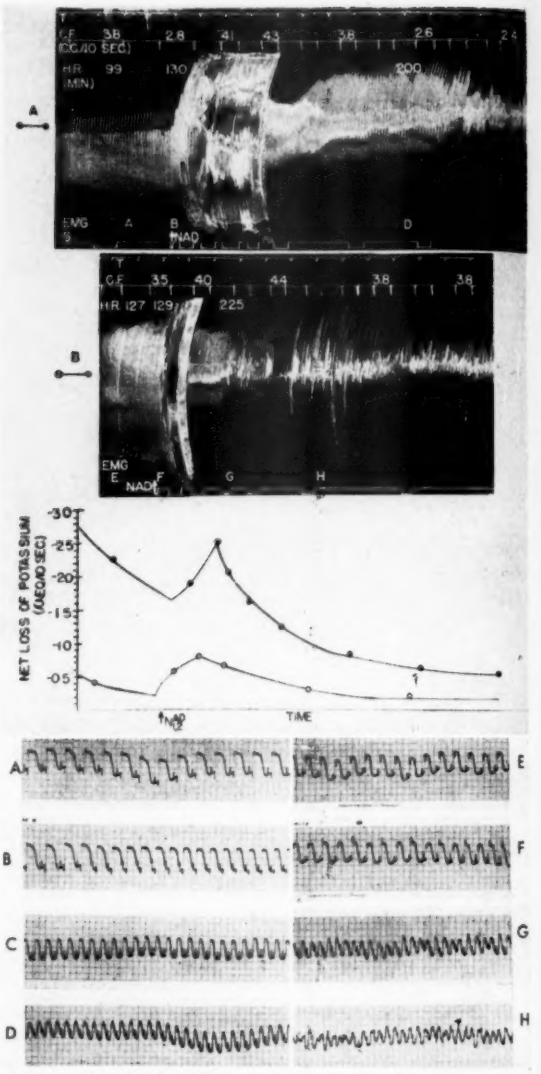

Fig. 8. Isolated rabbit heart perfused with potassium-free Locke's solution. (See legend, Fig. 2.) *Upper* and *Lower Kymograph Records* are continuous. The upper tracing was started 2 min after an injection of 25 mg of KCl (as in Figure 6). At each arrow, marked NAD, 100 μg of norepinephrine was injected. *Middle Graphs:* Calculated "potassium shifts" associated with above responses. *Lower Record:* Associated electrograms A to H, as marked on kymograph tracings above.

Locke's solution. Thus, there was a marked sinu tachycardia but no arrhythmias.

The lower kymographic record of Figure 7 shows the continuation of the experiment in which, while the heart was ostensibly contracting normally (despite continuous potassium-free perfusion), injection of epinephrine (ADR) immediately induced marked increase in coronary inflow associated with diminution of the contraction amplitude. However, as can be seen from the electrogram (G, lower record), there was an associated immediate outburst of paroxysmal ventricular tachycardia followed by multifocal ventricular ectopic beats. Subsequently, the heart contractions improved but the kymograph tracing still indicated gross irregularities, and as shown at H the multifocal ventricular pacemaker rhythm continued (although of lower voltage), along with a depressed S-T segment.

The middle graphs of Figure 7 show that following each injection of epinephrine, there was a

similar "net loss" of potassium from the heart, whether or not ventricular arrhythmias ensued. The initiation of these arrhythmias would therefore appear to depend on the existing degree of potassium saturation of the heart. Similar results were obtained in eight similar experiments, and the mean "net loss" of potassium following the epinephrine injections, under these conditions, was 6 μeq/10 sec. It would appear then that there is a relatively greater "net loss" than was observed during perfusion with either normal Locke's solution or Locke's containing 25 per cent of the normal potassium, as shown in Table I.

Rather similar results to those shown above were obtained in other experiments in which either norepinephrine (nine experiments), isoproterenol (six experiments), or aminophylline (seven experiments), were injected during perfusion with potassium-free Locke's solution. Typical examples of these results are shown in Figures 8 and 9 in which typical responses to norepinephrine and to aminophylline can be seen.

Immediately following the first norepinephrine injection (Fig. 8, upper kymograph record) there was an intense stimulation of the amplitude of the heart contractions and heart rate, associated with a transient coronary dilatation. These were rather potentiated responses, in comparison with those generally observed with norepinephrine during perfusion with normal Locke's solution, and as is evident, the electrograms (B, C, and D) showed only marked sinus tachycardia but no arrhythmias.

The lower kymograph record of Figure 8 shows the usual response to a second injection (NAD) of norepinephrine (without previous potassium resaturation). It is evident that already there was marked sinus tachycardia during the preinjection period (E), but following the norepinephrine there was an immediate transient further increase in heart rate and increased amplitude of contractions associated with increased coronary inflow, but within 40 seconds, obvious irregularities developed with a period of temporary mechanical arrest.

The electrograms recorded concurrently (E to H), showed that during the preinjection period (E), the normal pattern of electrical activity is still in evidence although the rate is somewhat increased (127 beats/min). Following the injection, there was a prompt shift in the P wave, probably a nodal pacemaker rhythm, as shown at F. Subsequently at G, there is an intense tachycardia (226 beats per minute) associated with A-V conduction changes (both prolongation and shortening) of the P-R intervals. Finally, associated with the gross mechanical irregularities, the electrogram taken at H showed definite ventricular fibrillation with occasional P wave deflections.

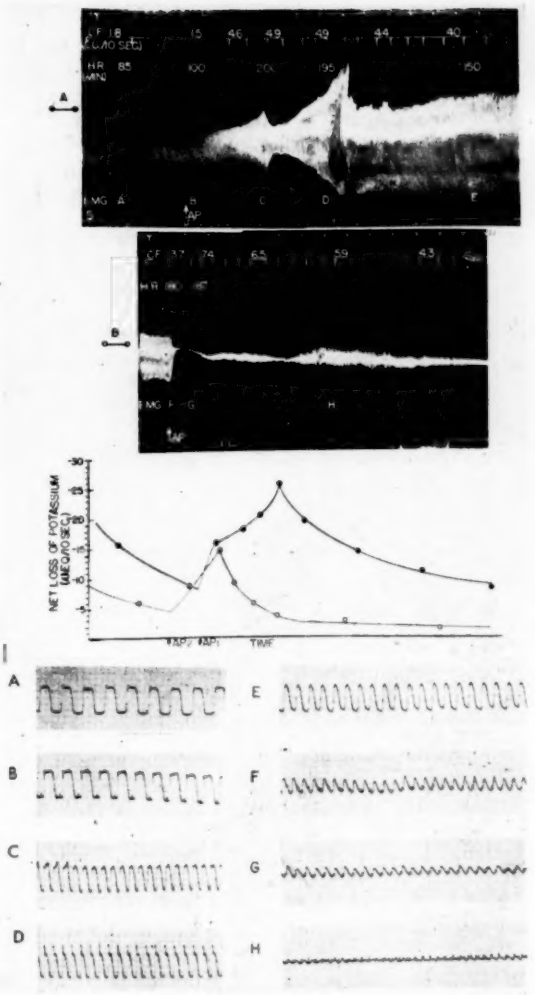

Fig. 9. Isolated rabbit heart, perfused with potassium-free Locke's solution. (See legend, Fig. 2.) *Upper* and *Lower Kymograph Records* are continuous. The upper tracing was started 2 min after an injection of 25 mg of KCl (as in Fig. 6). At each arrow marked AP, 6 mg of aminophylline was injected. *Middle Graphs:* Calculated "potassium shifts" associated with each of the above responses. *Lower Record:* Associated electrograms A to H, as marked on kymograph tracings above.

The concomitant potassium shifts associated with the above responses (middle graphs) indicate again that under both conditions of perfusion of the heart, injection of norepinephrine produced a "net loss" of potassium—the effect ensued whether or not cardiac irregularities were precipitated.

Similar results to those described above were obtained in eight other experiments, and the mean increased net loss of potassium following the norepinephrine injections, during perfusion with the potassium-free Locke's solution was 5.8 μeq/10 seconds. In contrast, when the heart was perfused with normal Locke's solution, the mean net loss was 2.02 μeq/10 sec, as shown in Table I.

Figure 9 shows effects of injections of aminophylline (upper and lower kymograph tracings) when the heart was presumably well supplied with potassium (above), conversely when the heart was losing potassium (below). As can be seen, the former injection led to a potentiated stimulation (amplitude and rate), while the latter induced a diminished amplitude of contractions with tachycardia and gross irregularities. However, again associated with each type of response there was a definite increased loss of potassium from the heart, as shown graphically in the middle section of the figure.

The electrograms of Figure 9 show that on continued perfusion with potassium-free Locke's solution, a slow and nodal rhythm with sustained ST segments developed (A). Following the first injection of aminophylline the normal pacemaker control was temporarily restored (B), and an intense and prolonged supraventricular paroxysmal tachycardia (C) ensued. This was followed by a period of nodal tachycardia (D) and tachycardia with aberrant conduction (F). Following the second aminophylline injection, there was continued tachycardia with aberrant conduction and increasing low voltage complexes, as shown at G and H. There was no definite electrical ventricular fibrillation recorded in these experiments, although the contractions of the heart were obviously irregular and feeble, as is evident from the mechanical record.

Similar results were observed in seven similar experiments, and the mean increased net loss of potassium following the aminophylline injections during perfusions with potassium-free Locke, was 5.83 μeq/10 sec, or approximately three times as marked as the mean potassium shift (1.87 μeq/10 sec) with this agent during perfusion with normal Locke (Table I).

Section II, conclusion of this paper, will be published in the August 1958 issue of this JOURNAL. *The complete list of references will be included in that section of the article.*

Review

The Anatomy of Chest Pain*

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PAIN is the most common of all symptoms. It is a warning signal against potential or actual damage to tissue cells. The thorax, especially the precordium, is one of the most frequent and confusing sites of this prime complaint (Tables I–V).

The increased frequency of precordial pain due to lengthening of the life span and the importance of differentiating cardiac from noncardiac pain cannot be overemphasized. It is the seasoned opinion of most competent observers that a good understanding of the origin and nature of this important symptom usually aids diagnosis more than any other single element.

Major dependence on some laboratory tests frequently proves misleading.[1] In some instances, the pain characteristics associated with some disorders are so diagnostic as to make a lengthy clinical appraisal unnecessary. This is typical of the severe tearing pain which occurs with most dissections along the aorta. However, various origins of precordial pain frequently bear a confusing resemblance to each other, especially at the onset. To complicate matters, it is not unusual for several factors capable of causing precordial pain to occur in combinations. Thus, the aged patient with advanced osteoarthritis of the spine, who is bedridden in a jack-knifed position because of coronary occlusion, may develop an aggravation of chest pain due to nerve root compression.[2] Occasionally, two "stress" conditions may occur simultaneously, e.g., squeezing upper substernal pain of angina pectoris which is relieved by nitroglycerin, and postprandial burning pain at the lower end of the sternum caused by peptic ulcer and relieved by antacids. Then there is the patient with chronic coronary insufficiency who suddenly develops marked aggravation of pain which arises in the center of the back, and which is suggestive of a posterior wall myocardial infarction. Four days later, characteristic herpetic lesions are discernible over the left side of the back.

A knowledge of the precise anatomy of the nervous innervation of the precordium and areas of referred pain is an invaluable aid in the differential diagnosis of precordial pain.[3–7] Unfortunately, investigation of the nervous system by anatomic methods has failed to give the complete answer to the intricate mechanisms by which cutaneous or visceral pain reaches the sensorium. Physiologic studies have carried the frontier of knowledge much farther. The ideal experimental subject is not the laboratory animal, but because of species differences, man himself.

Furthermore, different portions of the body vary widely in their sensitivity to pain and the stimuli whereby it is produced. Certain structures, such as the cornea, teeth and arteries, have little capacity for appreciating anything but painful stimulation. Other structures, such as the heart and lungs, usually present pain as the most important symptom. Pain may range from slight uneasiness to extreme distress. The threshold for its perception is defined as the lowest intensity of stimulus which is recognized as pain. A stimulus which causes pain in the skin may not produce pain in the heart. A pin-prick causes distress in the former, ischemia in the latter. It may have both emotional and

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physical components. The threshold of pain depends upon emotional stability, age, sex, past experiences, conditioned reflexes and other intangible factors.

Pricking painful sensations are conveyed by thick and rapidly conducting myelinated fibers. Burning pain is transmitted by small, slowly conducting fibers. Visceral pain is carried by myelinated and non-myelinated fibers which pass through the sympathetic chain. The afferent sensory fibers of the heart pass through this chain and enter the cord in the upper four or five thoracic posterior roots. They then pass into the spinothalamic tracts. Other thoracic structures, such as the aorta, esophagus, mediastinum and portions of the chest wall, possess sensory nerves with the same general afferent course (Fig. 1). The parietal pleura and diaphragmatic surface of the parietal pericardium are also pain sensitive but are supplied by the intercostal and phrenic nerves. The intercostal nerves also contain the pain fibers for the parietal peritoneum.

Pain from the skin can be sharply localized. Direct stimulation of the cutaneous nerves produces the same type of pain that arises from the skin. The intensity may vary but the quality is the same regardless of the stimulus (e.g., pinch, prick, burn, etc.). The quality of pain from deeper structures, such as the heart, differs from that of skin pain. It is longer lasting, more diffuse, and frequently radiates to a remote region. This is true of deep somatic structures as well as visceral organs. The distribution is segmental in part but may fill only a portion of

TABLE I

Chest Pain Arising from The Heart

A. *Coronary arteries*

Atherosclerosis, anomalies, infections (tuberculosis, syphilis), collagen disorders, aneurysm, embolism, neoplastic infiltration or compression, trauma, arteriovenous fistula, and diseases affecting the coronary ostia (syphilis, subacute bacterial endocarditis); coronary insufficiency (severe emotion or effort, hypertensive or thyroid crises, severe infections, arrhythmias, hypoxic states such as carbon monoxide poisoning or pulmonary diseases), angina pectoris, coronary thrombosis and postinfarction syndrome.

B. *Endocardium and valves*

Aortic stenosis or insufficiency, mitral stenosis, subacute bacterial endocarditis, post-commissurotomy syndrome, subendocardial fibroelastosis, ball-valve thrombus myxoma, ruptured sinus of valvasa.

C. *Myocardium*

Acute rheumatic fever (and other collagen disorders), hypertension, acute nonspecific myocarditis, trauma, acute cor pulmonale, thyrotoxicosis, severe anemias, amyloid disease, drugs and toxins, hypoglycemia ruptured ventricular aneurysm or interventricular septum.

D. *Pericardium*

Acute rheumatic fever (and other collagen disorders), specific pericarditis, acute nonspecific pericarditis, trauma, neoplasm, uremia chronic constrictive pericarditis.

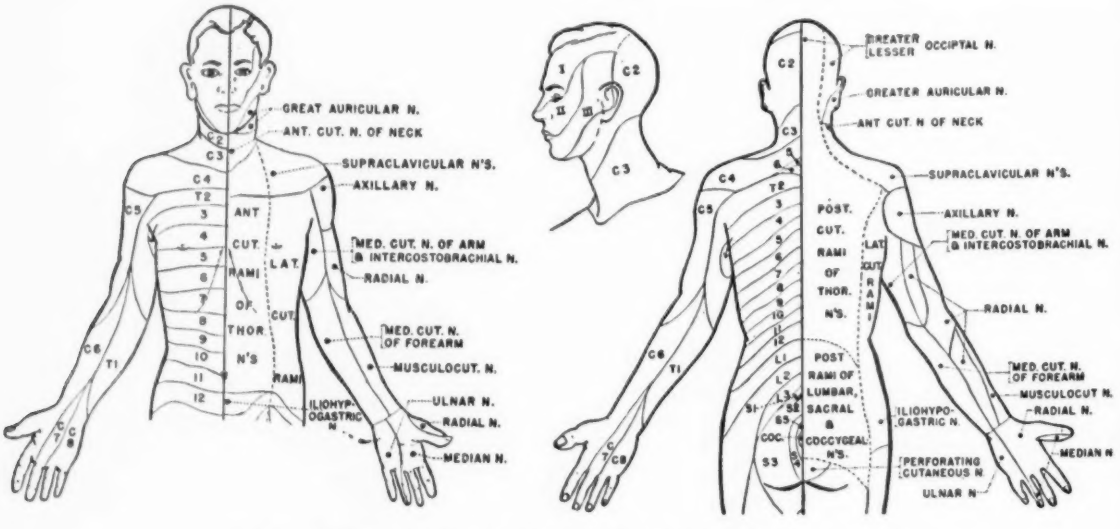

Fig. 1. Segmental innervations (Adapted from Wolff and Wolf[5]).

a segment, or overflow into adjacent segments. Hence, anginal pain may radiate down the inner surface of the left arm in the area which is innervated by C8 and T1 spinal segments. Some of the sensory nerves from the heart travel in the sympathetic chain and establish central connections at these cord levels. In some instances, referred pain is accompanied by superficial or deep hyperalgesia. It may be decreased by the injection of procaine or the spraying of ethyl chloride over this hypersensitive area.

Cardiac Pain (table 1)

Since the heart is a midline organ, pain is often referred to the retrosternal area and to one or both arms, although the reference is primarily to the left. Recent embryologic and clinical evidence suggests that the left chambers of the heart, pulmonary veins, and interatrial septum develop and receive their nerve supply from the left side. As the right auricle and right ventricle develop on the opposite side, disease involving these structures is likely to be referred primarily to the right. Thus in dextrocardia with accompanying angina pectoris, the pain is predominantly right-sided. Painful impulses from the heart travel along the sympathetic nerves, entering the sympathetic chains anywhere from the middle cervical to the 5th thoracic ganglion (Fig. 2). Here the fibers may travel up or down in the chain but enter the cord in the upper five thoracic roots. Characteristically, pain from the heart is felt beneath the sternum. Referred pain to the surface is localized mainly in the anterior portion of the 3rd to 6th thoracic segments with hyperesthesia involving the precordial area, and along the medial aspect of the left shoulder and arm in the distribution of T1

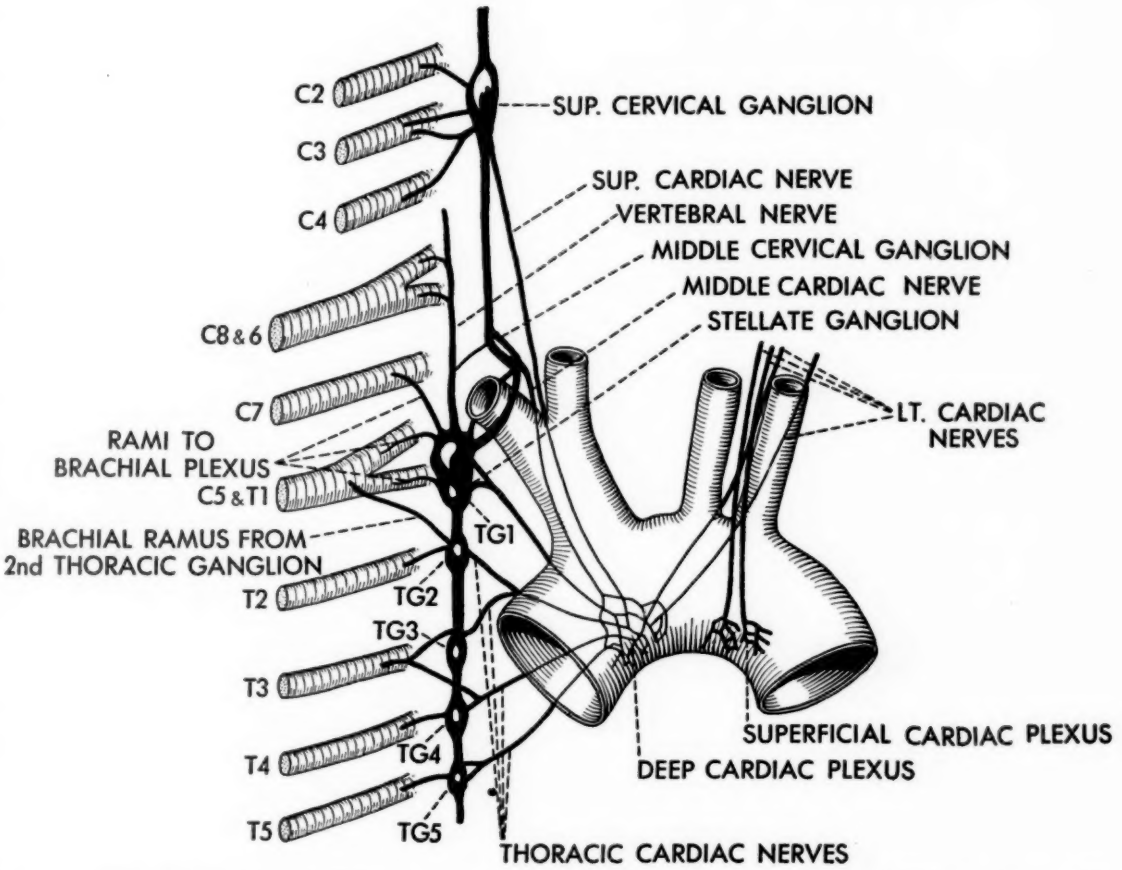

Fig. 2. Cardiac plexus and its connections (From Reich, N. E.: *Diseases of the Aorta*, Macmillan, New York, 1949, permission of The Macmillan Co.).

and 2. The area of reference of cardiac pain may, however, extend more widely from C3 to T10. Thus, it may be confused with pain arising from stimulation of other structures innervated by the same segment, notably the biliary passages, diaphragm, mediastinum, esophagus, apex of the lung, spinal cord, nerve roots and skeletal and muscular structures about the left shoulder and chest. When atypical cardiac pain reaches to the lower jaw it may suggest disease of the apices of the lower teeth. Roberts[8] has shown that pain referred from the heart is due to ischemia of the somatic nerves caused by spasm of the vasa nervorum. This mechanism

TABLE II

Chest Pain of Pleuropulmonary Origin

Pneumothorax, embolism, tumor, pleuritides, epidemic pleurodynia, eventration of diaphragm.

TABLE III

Mediastinal Origins of Chest Pain

A. *Esophagus*
Dysphagia, spontaneous rupture, esophagitis, diverticulum, peptic ulcer, carcinoma.
B. *Aorta*
Dissecting aneurysm, luetic aortitis, congenital defects.
C. *Tumors*
Substernal thyroid, thymoma, teratoma, lymphoblastoma, neurofibroma.
D. *Miscellaneous*
Mediastinitis, pneumomediastinum.

could account for the occasional relief of angina by local anesthesia, the occasional occurrence of silent infarction, the occasional disappearance of angina after infarction, the shoulder-hand syndrome or Dupuytren's contracture sometimes observed following myocardial infarction, and finally, the influence of psychic or stress situations on the precipitation of angina. Cardiac muscle hypertrophy results in a relatively decreased blood supply to the myocardium, but does not cause pain in the absence of other factors.

Pleuropericardial Pain (tables i and ii)

The visceral pleura does not originate pain impulses and thus is not pain sensitive. From the parietal pleura, pain sensation reaches the cord via the intercostal nerves. Hence, pains are felt in the area of the cutaneous segment immediately overlying the site of stimulation. This is true also of the portion of the parietal pleura reflected over the peripheral border of the diaphragm. Posteriorly where a considerable extent of the diaphragm lies against the chest wall, pain from the pleural surface may be felt in parts of the 7th to 12th thoracic segments including the lower thorax, lumbar region, epigastrium and even further down in the abdomen. For example the occurrence of pain has been described in the right lower quadrant of the abdomen with localized tenderness, cutaneous hyperesthesia in the region of McBurney's point, and spasm of the underlying muscles in certain instances of diaphragmatic pleurisy.

Stimulation of the central portion of the diaphragmatic pleura which is supplied by branches of the phrenic nerve gives rise to pain in the region of the trapezius muscle in the neck and shoulder (cutaneous distribution of the third and fourth cervical segments of the cord).

Phrenic nerve endings also supply the lower portion of the parietal pericardium and its stimulation also causes pain in the trapezius region. Noxious stimuli applied to the parietal pericardium at a distance from the diaphragm, however, do not induce pain. The frequent association of chest pain in acute pericarditis has been ascribed to stimuli reaching the pleural surfaces adjacent to the pericardium.

Pulmonary and Diaphragmatic Pain (tables ii and iii)

The lungs and bronchi originate embryologically as outpouchings from the primitive gut tube in the neck region. Fibers from the 3rd and 4th cervical segments are carried in the vagal rami to the cord in order to innervate it. Sensations arising from these structures are not necessarily referred to the cervical region, however, and are often correctly localized. Thus, in tracheitis the pain is felt beneath the sternum, and in centrally located bronchiogenic carcinoma pain may be felt in the chest immediately overlying the lesion.

Noxious impulses from the diaphragm travel mainly in the phrenic nerve, entering the cord in

the 3rd, 4th and 5th cervical roots. The peripheral portion of the diaphragm receives fibers from intercostal nerves and thus, as in the case of its pleural surface, painful stimulation of the muscle near its insertion will give rise to pain felt in the thoracic segments. Areas of reference for pain in the diaphragm may extend as far down over the abdomen and lumbar region as T12. For this reason, the pain of coronary occlusion has been closely simulated by diaphragmatic spasm.

Gastrointestinal Pain (tables iii and iv)

Diseases of the digestive tract are capable of producing pain in the lower chest or upper abdomen which may be confused with disease of many thoracic structures. In the gastrointestinal tract noxious impulses arise principally as a result of: (1) local stimulation of an engorged or inflamed mucosa, (2) distention or spasm of muscular elements of the tube, and (3) traction upon mesenteric attachments.

From the esophagus, impulses travel in fibers carried by the sympathetic nerves to the chains of sympathetic ganglia. From here they may enter the cord anywhere from the lowest cervical through the entire thoracic distribution.

TABLE IV

Chest Pain Referred from Abdominal Organs

A. *Biliary tract disease*
Dyskinesia, inflammation and stones, acute distension of liver capsule.

B. *Spleen*
Infarcts or rupture.

C. *Pancreas*
Inflammation and neoplasm.

D. *Gastrointestinal*
"Acute indigestion," distention (aerophagia, cardiospasm, and pylorospasm), hiatus hernia, carcinoma of fundus, gastric diverticula, peptic ulcer, colon flexure syndromes, carcinoid, dumping syndrome, abdominal migraine, peritonitis, retroperitoneal infections or malignancy.

E. *Adrenal*
Pheochromocytoma.

Whether or not the vagus participates in carrying afferent fibers which relay painful stimuli is still undetermined. The commonest pain from the esophagus is "heartburn," a burning pain felt substernally and fairly well localized over the site of stimulation. This pain is caused by cardiospasm. The commonest cause of heartburn in man results from the regurgitation of highly acid gastric juice into the esophagus which has already had its pain threshold lowered by the presence of engorgement or inflammation (esophagitis).

The pain of peptic ulcer which arises from the stomach or duodenum is frequently described as burning. It is of special interest that burning pain, ordinarily associated with noxious stimulation of the skin, can be elicited from the upper gastrointestinal tract. Hyperperistalsis, pylorospasm, antral distension, hyperacidity and inflammation augment the pain of ulcer.

TABLE V

Origins of Chest Wall Pain

A. *Cutaneous*
Lipomatoses, neurodermatoses, collagen disorders, deep cellulitis, thrombophlebitis, relapsing panniculitis, glomus tumors.

B. *Breast*
Gynecomastia, chronic cystic mastopathy, abscess, fat necrosis, occult carcinoma.

C. *Muscular* (extrinsic and intrinsic groups)
Strain or trauma, fibromyositis, collagen disorders, scapulocostal and scalenus anticus syndromes.

D. *Skeletal*
Fracture of ribs or vertebrae, displaced costal cartilage, costochondral syndrome (Tietze), arthritides of spine, slipped disc, collapsed vertebra (tuberculosis or cancer), tumors (osteochondroma, multiple myeloma, eosinophilic granuloma, metastatic), infections (osteoperiostitis), and xiphoidalgia.

E. *Neurogenic*
Cardiac neurosis, precordial migraine or epileptic equivalents, poliomyelitis, herpes zoster, nerve root compression (see skeletal), intercostal neuritis or neuralgia, tabes dorsalis, causalgic syndromes (classic, shoulder-hand, and anterior chest wall syndromes), cord tumors.

Impulses from the pancreas, liver and biliary tracts appear to travel in the same pathways as do those from the stomach. These facts indicate the difficulties encountered in the differential diagnosis of epigastric pain. Not only may it arise from the above structures but also from retroperitoneal tissues, skeletal muscles, or from lesions of the nervous system (such as herpes zoster or cord tumors) which involve dorsal roots. Epigastric pain may even be referred

TABLE VI

Example of Prepared Chest Pain Questionnaire Suitable for Office and Clinic (Courtesy, Master *et al. Ann. Int. Med.* 41: 315, 1954).

CHEST PAIN QUESTIONNAIRE

Name.....Date.....History No.....

Sex.....Age.....Occupation.....

COMPLETED BY.....(patient) or.....M.D.

INSTRUCTIONS: Please FILL IN EVERY SPACE ON THIS FORM, using check mark (V) for "yes" and zero (0) for "no." LEAVE BLANK ONLY IF UNKNOWN.

DURATION of chest pain or pressure.....years.....months.

TYPE:

Squeezing	Sticking
Constricting	Gnawing
Strangling	Aching
Compressing	Vise-like
Burning	Choking
Heaviness	Tightness
Pressure	Knife-like
Boring	Discomfort
Dull	Others

LOCATION OF PAIN OR PRESSURE:

Substernal (under breast bone)
Precordial (over heart in left lower chest)
Pit of Stomach
Back
Chest—entire.....left.....right
Other

DURATION OF PAIN OR PRESSURE: each attack.

Up to 1 minute
1 to 2 minutes
2 to 5 minutes
5 to 10 minutes
10 minutes to 1 hour
Over 1 hour
Continuous

FREQUENCY OF ATTACKS:

More than once a day
Once a day
Few times a week
Few times a month
Rare—Under once a month

RADIATION OF PAIN OR PRESSURE:

None
Back
Shoulder—both.....left.....right
Arm —both.....left.....right
Hand —both.....left.....right
Jaw
Neck
Other

ONSET:

Effort
Walking
Climbing
Emotion
Meals
Walking after meals
Cold
Walking in the cold
Walking against the wind
Spontaneous (no apparent cause)
Smoking
Intercourse
Fatigue
Lying down
Other

RELIEF OF PAIN OR PRESSURE:

	Relieves? *Yes* How many minutes?	*No*	*Not used*
Nitroglycerin			
Whiskey			
Rest			
Belching			
Spontaneous			
Other			

TOBACCO: .....Cigarettes / Cigars.....daily.

E.C.G.
"2-step"
"2-step"

B.C.G.—Normal.....Abnormal.....

REMARKS:

from the heart or other thoracic structures or from impulses arising in the lower bowel including the transverse colon and appendix. The hepatic parenchyma has been shown to be pain insensitive, but rapid distention of its capsule does give rise to pain. The same generalizations apply to other solid organs including the spleen and possibly the kidneys. Pain from distension of bile ducts and the gall bladder has been found to be commonly localized in the distribution of T9 either anteriorly beneath the right costal margin or posteriorly at the angle of the right scapula. Noxious impulses from the small intestine also travel in splanchnic pathways but enter the cord slightly lower than T9 to T11. The afferent innervation of the colon above the sigmoid is also carried in the sympathetic trunks.

Clinical Applications

The clinical application of these anatomic and physiologic facts will now be considered. An understanding of the distribution and characteristics of the pain is vital in the differential diagnosis of the numerous conditions which may cause thoracic pain (Tables I–V). The history should be elicited directly from the patient at

the time of the attack, if possible, without presenting leading questions. Since many patients are distraught at such times, they may agree to almost any question or may exaggerate its significance. The following characteristics of the pain should be elicited in each instance.

(1) *Location:* The exact area of pain should be delineated if possible. This may not be possible at all times, especially when radiation is prominent. In some instances (cardiac neurosis), the distribution of pain may be quite bizarre.

(2) *Depth and Intensity:* The depth and intensity of pain should be determined. Is the pain deep or superficial? Is it severe, moderate, or mild? The physician learns to evaluate the organic and superimposed nonorganic components from experience.

(3) *Quality:* The patient should describe the quality of pain in his own words. Is it heavy, boring, burning, pins and needles, wave-like, intermittent or continuous, pressing, sharp or dull, sticking, spreading, squeezing, etc.? Pricking, itching or burning pains arise from the skin. Burning pains arise also from the esophagus and stomach. Dull aching pains are more characteristic for deeper structures.

(4) *Duration and Frequency:* How long has this attack lasted? Is this attack abating or increasing? How often have such attacks occurred? Are they getting worse lately? Is there any regularity of recurrence? The recurring postprandial pain of peptic ulcer has a regularity and seasonal incidence not recognizable in other diseases. An anginal seizure lasts but several minutes.

(5) *Radiation:* Are any secondary areas involved or did the pain seem to move elsewhere? These areas should be mapped as carefully as possible since the major area of confusion lies in the evaluation of referred pains. An anginal seizure tends to radiate down the ulnar side of the left arm. It may also be referred to either shoulder, neck, jaw, lower teeth and back.

(6) *Factors Which Influence Pain:* Most pains may be noted to begin or to become aggravated or to improve under certain specific circumstances. Careful questioning frequently proves highly rewarding in establishing the diagnosis. Walking uphill against a cold wind is a common description of a precipitating factor in angina pectoris. The fact that it is quickly relieved by nitroglycerin or rest is equally characteristic. Pleuritic pain is influenced by coughing or breathing. Spinal root lesions are aggravated by coughing, straining or sneezing. Analgesics reduce the intensity of most pains when taken in sufficient dosage. This does not aid much in differential diagnosis unless one takes into account the potency of the drug and its dosage. A tablet of aspirin may relieve intercostal neuralgia, whereas dissecting aneurysm may remain unrelieved following huge doses of opiates.

(7) *Associated Symptoms and Findings:* The appearance of other symptoms and findings may prove diagnostic. For example, coexisting cyanosis, dyspnea, and feeble heart sounds would be expected to occur in coronary occlusion rather than in intercostal neuritis. However, the subsequent appearance of a pericardial friction rub may make it difficult to differentiate between acute pericarditis and coronary occlusion without the benefit of other findings and studies. Considerable time and effort may be saved in office practice by having the patient fill out a prepared questionnaire (Table VI) prior to examination.[9]

Summary

In summary, it may be stated that the pitfalls in the differential diagnosis of precordial pain are numerous. Meticulous attention to the anatomy and mechanism of various pains as well as proper history taking in clinical application will minimize the possibility of error in diagnosis.

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Case Reports

Uncomplicated Congenital Mitral Stenosis*

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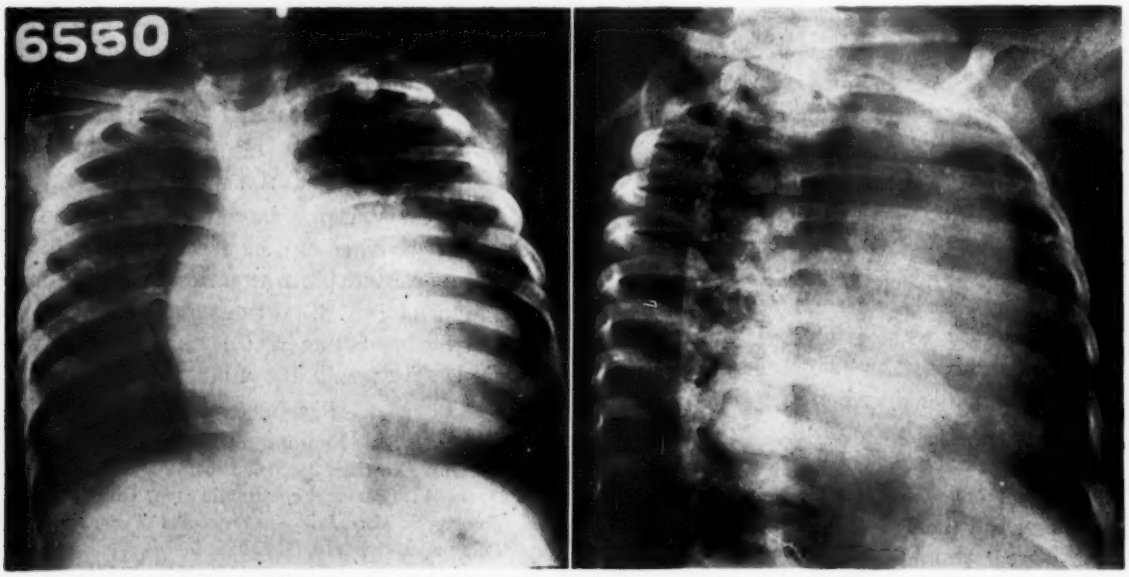
THE DIAGNOSIS of congenital mitral stenosis was for many years of only academic interest since there was nothing that one could do about it. The major discussions were those of the pathologists and embryologists who attempted to explain the anomaly and describe it merely for the embryologic and pathologic interest. With the present development of cardiac surgery there presents itself now the possibility of curing this congenital lesion, if the diagnosis can be made. We are, therefore, reporting a case of congenital mitral stenosis, the diagnosis of which was made clinically and confirmed at operation and at autopsy.

CASE HISTORY

M. B., a 17-month-old male child, born September 21, 1953, was delivered by low forceps, vertex, with saddle anesthesia. The baby cried spontaneously. No resuscitation was needed. Physical examination immediately after delivery was not remarkable. No cardiac signs or symptoms were noted at this time.



A B

Fig. 1A. Posteroanterior 3 foot film showing heart size and contour (see text). (B). Right anterior oblique view of heart.

CLINICAL COURSE AND FINDINGS

When the baby was about one month old, the parents noted that the heart beat rapidly. Their physician noted a murmur at that time but told the parents that it was of no moment. The baby's development was normal, but weight gain was slow. Cyanosis or dyspnea was not noted.

About five months before admission, the parents noted that the baby began to have sweats and bouts of rapid

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Fig. 2. The electrocardiogram taken at the time of the first admission showing the P-pulmonale.

breathing. X-ray examination of the chest at that time showed an enlarged heart but no further workup was done nor was any therapy or follow up suggested.

The child was first seen by us at 15 months of age with complaints of sweats and dyspnea. A diagnosis of congenital heart disease was made and the baby was admitted to Newark Beth Israel Hospital for definitive studies. The positive physical findings at this time were as follows: There was a sinus tachycardia with the rate varying between 100 and 150 per min. A systolic murmur was heard and thrill palpated over the entire precordium. The murmur was loudest at the apex and in the mitral area. The murmur was also heard posteriorly at the left scapula. P_2 was accentuated over A_2.

X-ray showed enlargement of the right ventricle with elevation of the apex of the diaphragm. The right auricle was also enlarged. There was a suggestion of a double contour shadow on the right border of the heart as seen with enlargement of the left auricle. The pulmonary artery was prominent. There were increased hilar markings indicative of congestive heart failure. (Fig. 1.)

Following jugular venipuncture the patient suddenly became cyanotic and very dyspneic, but recovered rapidly. The following morning, however, the patient was found to be in congestive heart failure with dyspnea, orthopnea, cyanosis. and a palpable liver, none of which had been present on admission. The response to oxygen, digitalization, and mercurial diuretics parenterally was excellent.

The electrocardiogram showed peaked, notched and wide P waves, suggestive of P-pulmonale. The electrical position was intermediate. The rest of the electrocardiogram was considered normal for this age group (Fig. 2).

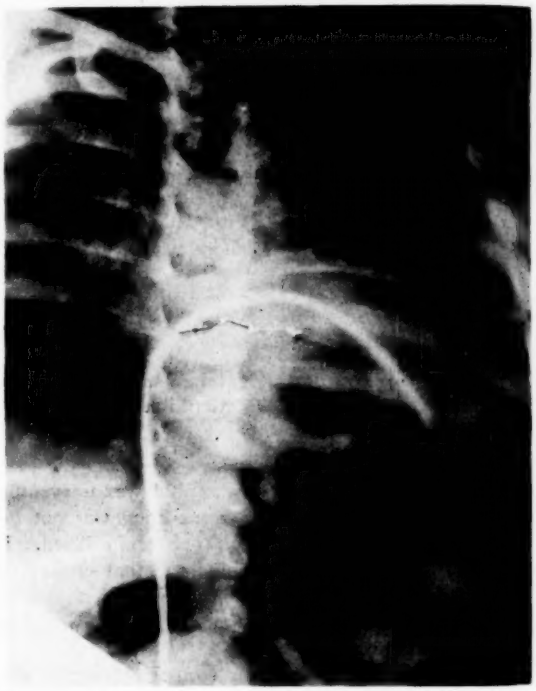

Fig. 3. This spot film shows the tip of the catheter in what appears to be the left ventricle but which was later found to be the pulmonary conus which was dilated and hypertrophied.

Ten days after admission catheterization of the heart was performed. The catheter was inserted through the right saphenous vein and passed into the right auricle through the inferior vena cava. Pressures in both cavae, right auricle and right ventricle were normal, as were the oxygen saturation levels. The pulmonary artery could not be entered in spite of repeated efforts. At one point the catheter seemed to enter the left ventricle, but this was not confirmed by pressure or oxygen studies (Fig. 3).

Since catheterization failed to give a diagnosis, angiocardiography was performed one week later. Diodrast ® 70 per cent was injected in 10 cc quantities into the left median basilic vein and x-rays were taken in the left anterior oblique and right lateral positions. The angiocardiograms showed a definite hold-up of the dye for 7 sec at the mitral valve, and a diagnosis of congenital mitral stenosis was made (Fig. 4).

Fig. 4A. Angiocardiogram taken at 2 sec after injection of the dye with the patient in the left anterior oblique position.

The patient's course in the hospital was uneventful once he was digitalized, and his condition was not altered by any of the diagnostic procedures utilized. It was decided that he be sent home and that surgery be postponed as long as possible since it was felt that if he were bigger and stronger his chance of survival would be markedly improved.

Three weeks later, because of recurrent heart failure, in spite of adequate therapy, the patient was readmitted to the hospital. After three weeks in the hospital, it was found that medical therapy was less and less effective. Therefore, surgery was performed on February 14, 1955. The patient did poorly during surgery and two hours postoperatively there was sudden cardiac arrest. The chest was opened immediately and cardiac massage and oxygen under positive pressure were continued for one hour to no avail.

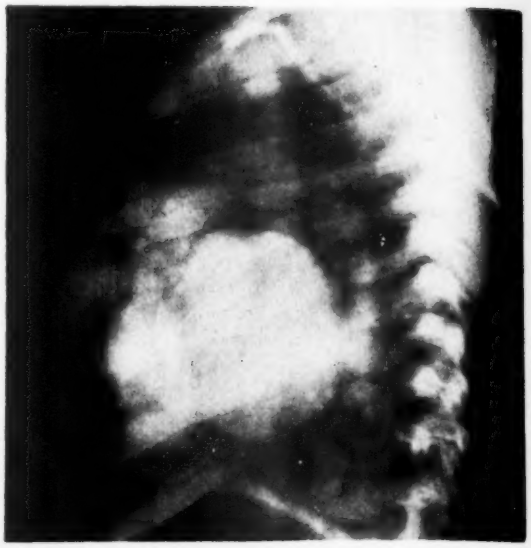

Fig. 4B. At the end of 4 sec the left auricle is filled but there is no dye in the left ventricle.

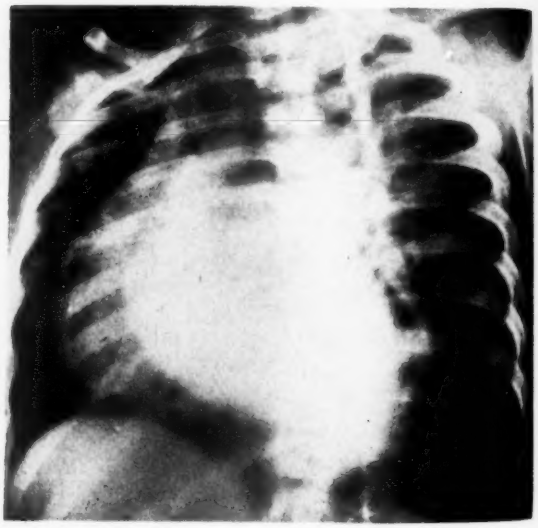

Fig. 4C. At 5 sec the left auricle is still heavily opacified with dye, with the left ventricle just beginning to fill.

OPERATIVE FINDINGS

The chest was entered through a 4th interspace lateral thoracotomy. As soon as the chest was opened the heart was seen to be beating very feebly and irregularly. Since it was felt that the difficulty was mechanical obstruction to the passage of blood into the left ventricle, either in the form of a congenital mitral stenosis or of a transverse

partition across the left auricle forming a cor triatriatum, it was decided to proceed at once to attempt to relieve the mechanical obstruction before the heart failed completely. A purse-string was rapidly placed around the small left auricular appendage. The auricle itself was enormous, most of the enlargement being posterior to the pulmonary veins. The pulmonary veins were very large. An incision being made into the appendage and the 5th finger inserted into the auricular chamber through the appendage, an enormous auricle was found. There was no difficulty in passing the finger straight back into the huge auricular chamber, and the mitral orifice was found medially and anteriorly. The little finger, which was employed, fit the valve very snugly. The heart had almost stopped beating so subsequent manipulations were frequently interrupted by the necessity for massaging the heart and restoring its mechanism. Adrenalin 1:10,000 and 10 per cent calcium chloride were injected into the heart on a number of occasions. The heart fibrillated only once and then returned to a regular rhythm with massage. In all, there was a period of about ten minutes during which the heart was maintained solely by massage.

Communication with the right side of the heart was not found, and no one actually hooked his finger around into the pulmonary veins, although there seemed to be no question but that the auricular chamber we were in was the one which communicated with the pulmonary veins. We had been prepared to take pressures in the auricle and simultaneously in the ventricle, but the rapid development of events prevented this. With the finger the opening in the mitral valve, which was rubbery and firm, was dilated until the 5th finger fit fairly easily. However, the valve never gave. The heart was beating poorly during all this time, but there was never at any time regurgitation through the valve, and the valve leaflets just felt like a firm, smooth floor to the auricle. There was no ballooning of the valves. The most striking thing was the marked medial and anterior displacement of the opening and the rubbery consistency of the edges. An attempt was made to pass the guillotine knife in without the finger, but we were never sure of the position of the knife and therefore did not cut the valve edge.

In view of the fact that the heart really had not beat properly since before the pericardium was opened, and the dilating instruments could not be successfully passed into the opening, it was decided to desist. The purse-string suture was pulled taut and the appendage oversewn.

Postoperative Diagnosis: Giant left auricle, congenital mitral stenosis.

AUTOPSY FINDINGS

Gross Description: The heart is large, weighing 119 g (normal 48 g). All chambers are enlarged, especially the left atrium and right ventricle.

The right atrium is moderately hypertrophied. Its endocardium is widely and irregularly opaque, but smooth and lustrous. The tricuspid valve is intact. It measures 5.3 cm in circumference. The right ventricle is moderately hypertrophied, its wall measuring 0.5 cm in thickness. The interventricular septum bulges to the right. The endocardium is smooth, lustrous, and transparent. The most striking feature is a marked dilatation and hypertrophy of the pulmonary conus projecting anteriorly behind the anterior tricuspid leaflet of the tricuspid valve (Figure 5). This formation is

Fig. 5. This shows the right ventricle, the tricuspid valve, and the "accessory ventricular cavity."

marked off from the right ventricle proper by a sulcus on the epicardial surface. The measurements of this "accessory ventricular cavity" are 5.5 × 3.5 × 1.5 cm. The pulmonic valve is intact. It measures 3.7 cm in circumference.

The pulmonic veins enter the left atrium normally. The left atrium is markedly dilated and thick-walled. Its endocardial lining is opaque, gray-white in color, but smooth and lustrous (Fig. 6). The auricular appendage has been partially resected and is sutured closed. The mitral valve is strikingly stenotic, admitting one finger through a tight ring (Fig. 7). It also appears to have been insufficient. There is a fusion at the commissures. The valve cusps are thickened throughout. There is no calcification. The anterior cusp is large, but deformed by fusion and thickening. The posterior cusp is narrowed, shortened, and irregular. Some indentation and protuberance are present at the cusp surface caused by fibrosis, but no vegetations. The chordae tendineae are greatly distorted. Several on each side run almost horizontally to attach to the posterior and anterior left ventricular walls. These are shortened and

Fig. 6. This shows a probe in the mitral valve. The atrium is dilated and thick-walled with an endocardial lining that is smooth but opaque.

Fig. 7. This shows the stenotic mitral valve with fusion at the commissures as seen when looking down from the atrium. The anterior cusp is large and deformed and there is narrowing and shortening of the posterior cusp.

thickened, fusion apparently having occurred, forming two heavy bands (0.3 cm thick) on the posterior end and a heavy band (1 × 1 × 0.3 cm) on the anterior end of the anterior cusp (Fig. 8). On the posterior end, the chordae run into a rudimentary papillary muscle high up on the ventricular wall. There is no vestige of an anterior papillary muscle and over most of the valve free edge no chordae can be made out. The mitral valve orifice measures approximately 1 cm in diameter and 4 cm in circumference along the free edge. Along the

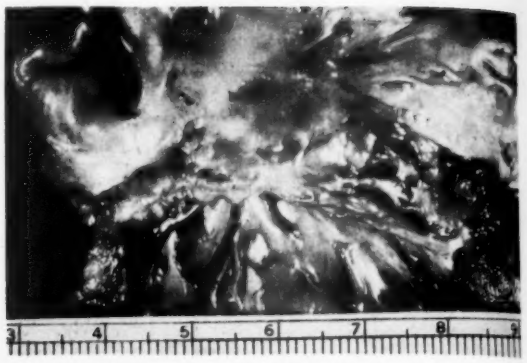

Fig. 8. This is a close-up of the mitral valve showing the distortion of the chordae tendineae as well as the irregularities of the valve edge caused by fibrosis. There are no vegetations.

Fig. 9. This shows the entire left side of the heart. All the relationships described in the text are demonstrated as well as the thickening of the endocardium of the ventricle and the fibrosis of the trabeculae carnae.

ring the valve circumference measures 4.8 cm in thickness. The endocardium is thickened and opaque at the apex and in the outflow tract. Elsewhere, it is more translucent. In the outflow tract the trabeculae carneae appear fibrotic (Fig. 9). The septa are intact. The foramen ovale and ductus arteriosus are closed.

The aortic valve is normal. It measures 3.1 cm in circumference. The coronary artery ostia are normally situated. The aorta is rather small. It measures 2.9 cm in circumference in the ascending and 2.2 cm in the descending portions. The pulmonary artery seems somewhat dilated, measuring 4 cm in circumference.

Microscopic Description: Lungs: Atelectasis and bronchial collapse are present with intense congestion and focal hemorrhage. Macrophages are noted in the collapsed alveoli as well as peribronchial lymphocytic aggregates. One pulmonary artery branch shows an endocardial fibrous hillock containing a multinucleated giant cell. There is no thickening of either arteries or arterioles.

Heart: The mitral cusps are short and thickened by a cellular, fibrous tissue. A deposition of calcific fragments is present in the valve ring. Also, just below the valve ring of the anterior cusps, there is a fibrous hillock with calcific fragments beneath the endocardium. There is fibroblastic thickening of the left auricular endocardium with disappearance of smooth muscle. Subendocardial hemorrhage is present over the left ventricular side of the septum. In one section of the left ventricle there is thickening of the endocardium and diffuse fresh hemorrhage. At one point adjacent to the pulmonary conus, in the epicardial wedge below the tricuspid valve, there is a collagenous nodule containing calcific fragments.

Adrenal: No cortical lipid.

Anatomic Diagnosis: (1) Congenital mitral stenosis and insufficiency (probable post intrauterine endocarditis). (2) Status four hours postcardiotomy (left auricular appendage) and dilatation of the mitral valve. (3) Bilateral pulmonary atelectasis.

Cause of Death: Pulmonary atelectasis, postoperative shock.

PATHOLOGIC SUMMARY AND CONCLUSION

This was a case of "pure" congenital mitral stenosis. No patent ductus nor interauricular or interventricular septal defects were present. There was left ventricular hypertrophy and dilatation possibly indicating mitral insufficiency. Unexplained was a marked selective dilatation of the pulmonary conus. Endocardial thickening was prominent only in the left auricle. Focal microscopic calcification of the mitral ring and subvalvular endocardium was present, suggesting an inflammatory process.

Discussion

All of the reported cases of congenital mitral stenosis were reviewed by Ferencz *et al.* in 1954[1] except for one case of Bower *et al.*[2] which they missed. They summarized 34 cases and then added nine of their own. This brought the sum total in the world literature to 44 cases.

All readers are referred to this excellent paper for a careful analysis of the reports up to the date of their publication. Maxwell and Young[3] reported one case, followed by Kjellberg *et al.*[4] who reported on one patient from their group in Stockholm. Most recently, Braudo *et al.*[5] reported two cases from their clinic in Johannesberg, South Africa, bringing the sum total of reported cases of congenital mitral stenosis uncomplicated by interauricular septal defect to 48. We shall not in this paper discuss the so-called Lutembacher syndrome, which combines congenital mitral stenosis with an interauricular septal defect. This condition is so well established and presents its own clinical entity and therefore has been separated from the other cases of congenital mitral stenosis which may or may not have other anomalies associated with it.

Of the 48 cases presented in the literature, only 10 were uncomplicated by other congenital lesions. Most of these other lesions involved the aortic arch and the ductus arteriosus. The presence of these other anomalies often made the diagnosis much more difficult.

CAUSES OF CONGENITAL MITRAL STENOSIS

Fibroelastosis: Many, if not all, of the cases showed evidences of fibroelastosis. The question of whether the fibroelastosis is primary or secondary has never been finally settled. The fibroelastosis has been found both in the atrium and in the ventricle. It is possible that if it is present in the atrium alone that it is secondary to the mitral stenosis, but, when it involves the ventricle, one must consider it to be primary, unless there is an associated aortic stenosis. Probably, therefore, fibroelastosis is a primary condition rather than a secondary one and is related to the same factors that produce the congenital mitral stenosis rather than being secondary to the back pressure from the stenosis itself.

Embryonic Maldevelopment: Bower[2] has suggested that congenital mitral stenosis is due to unequal division of the common atrioventricular canal. This question, of course, has yet to be settled, but this suggestion is an intriguing one. In most of the cases, the normal valve cusps are replaced by a funnel-shaped structure which seems to extend down into the left ventricle. The valve cusps are thickened and seem to have a cartilage-like consistency. The chordae tendineae are often deformed, short, and quite thick. However, none of these findings are universal and there are slight variations

in each case. The amount of fibroelastosis present also varies markedly and is almost absent in some and is quite apparent in others.

Donnelly[6] has pointed out that as a result of the congenital mitral stenosis there is also interference with the development of the left ventricle. He notes that at one point the valves are formed from endocardial as well as muscular structures. It is at the point that the musculature in the valve structure is supposed to degenerate that there is an interference with the normal division of the valve into segments. There is, then, an interference with and an arrest of growth, not only of the valves but of those parts of the heart which depend upon the proper functioning of these valves. This must occur somewhere before eight weeks of embryonic age, since it is at this point that most of the heart structures are formed. The importance of this failure of development of the left ventricle lies in the fact that when the left ventricle is very small there is danger in surgical intervention, since opening of the mitral valve will throw a load upon the left ventricle which it is incapable of handling. This will cause heart failure and will certainly hasten death rather than help the patient.

Fetal Endocarditis: In the case herein presented, it was pointed out in the discussion of the pathology that there were lesions present suggesting that a fetal endocarditis might have played a role in the fusion of the valve cusps rather than congenital failure of the valve to separate into its component parts. The finding of calcified areas in the mitral valve is certainly highly suggestive of an endocarditis as a possible etiologic factor. However, it was pointed out by Bower *et al.*[2] that this was a common source of discussion in the literature for many years. They think that it is not a fetal endocarditis which causes the cusps to fuse, but it is much more likely that the fibroelastosis, so commonly found, is the major factor in preventing the proper embryologic development. There is, then, a failure of cusp formation rather than fusion after formation. This problem comes up mostly in the isolated cases of congenital mitral stenosis and is rarely a source of controversy in those cases where there are many other congenital anomalies in the heart. For the present our own case merely adds to the confusion rather than helps solve it, because in this case the areas of fibroelastosis are present, and, furthermore, there are evidences suggestive of fetal endocarditis as well. Under the circumstances then, we are forced to conclude from our own findings that one or the other or both played a role in this case.

CLINICAL COURSE

In reviewing the cases of uncomplicated congenital mitral stenosis, the clinical course of most of them parallels that of our patient. Though some of them have trouble from birth, others do not have difficulty until the second year. Our patient had a rapid heart beat starting at one month and failed to gain well from birth, but it was not until he was one year old that his real symptoms began. Usually, failure of development and then dyspnea are the presenting symptoms.

On examination the heart enlargement and evidences of heart failure are found. The most interesting sign is that of a systolic murmur at the apex, usually of grade 2 to 3 intensity, which may be accompanied by a systolic thrill. Presystolic or diastolic murmurs may be heard in the 2nd or 3rd interspace just to the left of the sternum. This finding of systolic murmur at the apex may help in differential diagnosis. If a presystolic or diastolic murmur is present the diagnosis is less difficult. The second pulmonic sound is usually accentuated and cyanosis is not present or is related only to crying.

On x-ray examination the heart shows enlargement of the left atrium and, at times, of the right one as well. The right ventricle is usually enlarged and the left ventricle may be small, normal or enlarged. The angiocardiogram in the case of Braudo *et al.*[5] and in our case showed a marked hold-up of the dye at the mitral valve. This may very well be one of the best diagnostic signs we have of this condition.

The electrocardiogram often shows right ventricular hypertrophy as well as atrial hypertrophy. However, the electrocardiogram in our patient failed to show the ventricular hypertrophy though the P-pulmonale was present.

The prognosis of the patients with uncomplicated congenital mitral stenosis is poor, since

eight of the ten reported cases died before the age of two years. This means that it is vital that the diagnosis be made as soon as possible and that surgery be attempted.

In differential diagnosis, patent ductus arteriosus, auricular and ventricular septal defects, the Eisenmenger complex, pulmonary stenosis, and idiopathic pulmonary hypertension must be considered. Cardiac catheterization and angiocardiography will almost always differentiate the congenital mitral stenotic from the group mentioned above if the clinical findings alone are not enough as outlined.

SURGICAL INDICATIONS AND RESULTS

Some of these cases have lived for longer periods of time without developing heart failure, but most of them, as has been pointed out, begin to have difficulties early in life and eventually show evidences of heart failure and need help. We tried to carry this child along for some months in the hope that the child would grow more so that the surgery would be less difficult. However, in spite of digitalization and use of mercurials and low-salt diet, the child continued to get into trouble at such frequent intervals that it was felt that surgery was a necessary life saving measure. Unfortunately, in this case the burden of the anesthesia itself was almost sufficient to cause death since the heart was already found to be beating irregularly and ineffectively upon entrance into the pleural cavity. Failure to effect quickly a considerable increase in blood flow across the mitral valve and the periods of ineffectual ventricular contraction which necessitated cardiac massage undoubtedly contributed to the severe generalized anoxia which finally resulted in shock and death.

The postoperative pulmonary atelectasis added to the difficulties in oxygenation, producing further cerebral and generalized anoxia. Actually then, one might say that the child never recovered from the anesthesia.

It would have seemed that our patient presented the proper conditions for surgery to have been of benefit. The left ventricle was not atretic, but was in fact somewhat enlarged and hypertrophied, as was the right ventricle. The left auricle showed evidence of being almost a "giant" left auricle. Yet the atrial appendage was far too small to form the capacious operating funnel one enjoys in the adult variety of mitral stenosis. In retrospect, it would have been of great advantage to have placed an additional purse-string suture isolating a small segment of the auricular wall itself close to the atrial appendage and to have used this controlled aperture to introduce the cutting instrument for the mitral valve. In this manner accurate placement of the instrument could then have been achieved by palpating and directing with the finger introduced through the more usual appendical aperture.

Even if this procedure had been followed in this case, commissurotomy was probably doomed to fail no matter how well and carefully it was done. In view of the malformation of the chordae as well as the valve structure as found at autopsy, even if the valve had been accurately and sufficiently cut, it is probable that severe regurgitation would have followed the retraction of the fibrous leaflets and chordae. This would indubitably have led to the same fatal outcome in due course of time. Though at autopsy the possibility that there might have been some regurgitation as well as stenosis presented itself, the surgeon was unable to find any evidence of regurgitation at the time of the operation.

Of the four previously reported cases of valvulotomy for congenital mitral stenosis, only two had successful outcomes. The first case of Bower *et al.*[2] operated on in 1952 (finger fracture only), survived at least seven months postoperatively even though no commissures could be palpated and biopsy of the valve showed fibroelastosis. Diastolic murmurs only were heard postoperatively. Their second case died 36 hours postoperatively (Brock's valvulotome used) and here, too, fibroelastosis was found at autopsy. The patient of Maxwell and Young[3] died suddenly six weeks postoperatively and in this case the valve showed fibroelastosis. Braudo *et al.*[5] operated on a three-month-old child (finger fracture of the valve) with a successful outcome for at least 16 months thereafter.

Apparently, the lack of commissures and the presence of fibroelastosis do not preclude a successful result, at least for the length of time

these cases were observed. It is truly surprising that fracture could be achieved and no regurgitation result and yet this is what happened. Bower *et al.*[2] believe that success or failure in surgery depends on whether the case is one of "pure mitral stenosis" or if it is of the "unequal division type." The former, they believe, can be helped, the latter will succumb because of the poor aortic and left ventricular development. Though their patient who died had a normal left ventricle and aortic valve, suggesting that other factors may also play a role, their theory may still be valid at times. The presence of fibroelastosis in almost all these cases itself suggests the fact that all of these patients are poor risks and that at this time with the paucity of material for analysis, it is too soon to set up criteria for selection of cases or to be very hopeful of the ultimate outcome.

We can, however, safely conclude that in these small babies, in poor condition, commissurotomy must be effected expeditiously using an auxiliary atrial opening to aid instrumentation if needed. Finally, in view of the deformed chordae as well as the peculiarities of valve formation, the results might be better with surgery under direct vision using an extracorporeal circulation.

Conclusions

Pure mitral stenosis presents, then, problems in embryology, etiology, pathology, diagnosis and in surgical technic which must all be constantly re-evaluated by all who see these cases so that eventually we may accumulate a statistically significant group from which some valid conclusions may be drawn. We do not have the temerity on the basis of one case and a review of the literature to take sides in the pathologic and embryologic discussions nor to outline criteria for selection of cases for surgery nor to outline a final surgical technic. A high index of suspicion for the condition in the noncyanotic child in failure with a murmur at the apex, and a medical and surgical team with humility and regard for the patient, will ultimately rehabilitate a higher percentage of these cases than we have been able to do so far.

Summary

(1) A case of congenital mitral stenosis uncomplicated by other congenital defects is reported.

(2) The diagnosis and differential diagnosis of this condition are outlined.

(3) The possible causes and the pathology of the condition are presented.

(4) The problems of the surgical correction of this lesion are described and considered for future use.

Acknowledgments

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Wolff-Parkinson-White Syndrome and Tetralogy of Fallot*

Report of a Case

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THE WOLFF-PARKINSON-WHITE syndrome is a peculiar electrocardiographic finding, characteristically recognized by a short P-R interval and broad QRS complexes with a slurred upstroke of the R waves (delta waves).

There have been many theories suggested to explain this syndrome.[1–3] At the moment the most acceptable is the one presented by Sodi-Pallares and associates.[4] For these authors the mechanism of the Wolff-Parkinson-White phenomenon implicates the existence of an area in the higher parts of the interventricular septum which does not offer a normal resistance to excitability. As a consequence, the ventricular activation begins early, starting in the high septum instead of having its normal origin in the lower regions. They also demonstrated that there exist two specific sensitive points in the septal tissue: one near the pulmonic valve, giving rise to the Wolff-Parkinson-White syndrome type A, and another close to the tricuspid valve, responsible for the type B.†

This syndrome is considered to be rare, its incidence being in the range of 0.1–0.2 per cent. About 60 per cent of the individuals showing this electrocardiographic phenomenon are normal (at least apparently), as far as cardiac diseases are concerned. Among patients presenting cardiopathies, the existence of Wolff-Parkinson-White syndrome has been more constantly found in cases of arteriosclerotic heart disease. In children with congenital malformations, this syndrome has been described as commonly associated with the Ebstein's anomaly, to such a point that Sodi-Pallares[5] stresses: "We have never seen the combination of Wolff-Parkinson-White syndrome type B and cyanosis, except in Ebstein's disease." This author also points out the association of this syndrome type A to interventricular septal defects. Recently, Hejtmancik and Herrmann[6] reported this syndrome in six patients with congenital heart disease. In four of them the diagnoses of the malformations were mentioned; these were: fibroelastosis, transposition of the great vessels, interventricular septal defect and Ebstein's disease. These authors did not point out, however, what type of syndrome (A or B) the patients showed.

It is our purpose to present a case of tetralogy of Fallot with persistent Wolff-Parkinson-White syndrome. As far as we know, this association has never previously been described.

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† These two types of Wolff-Parkinson-White syndrome, as described by Sodi-Pallares, are as follows: Type A: ÂQRS approximately +90° in the frontal plane; there are no QS complexes in leads 2, 3, and aVF; the QRS complexes are mainly positive in right precordial leads and negative in the left ones. Ventricular activation takes place from the posterior to the anterior part of the chest. Type B: The ÂQRS is directed to the left; QS complexes are frequent in leads 2, 3, and aVF; QRS complexes are negative in the right precordial leads and positive in the left ones. Ventricular activation takes place from the anterior to the posterior part of the chest.

Case History

The patient, M. M., a seven-year-old white boy, was admitted to Saint Vincent Charity Hospital on February 6, 1957. His history revealed cyanosis since birth. The physical examination showed an underdeveloped child, presenting marked cyanosis of the lips, ears, nose and extremities. The heart was enlarged to the left, a systolic thrill was palpable at the pulmonic area, the 2nd sound was low and a harsh, systolic murmur grade V was heard over the whole precordium, particularly at the second left intercostal space. X-ray examination of the chest in the P-A and oblique views with barium swallow revealed cardiac enlargement without any prominence of the pulmonary artery; the lungs were normal (Fig. 1).

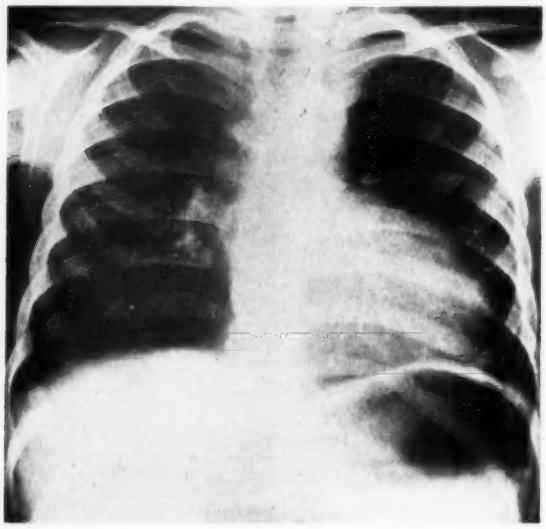

Fig. 1. Chest x-ray shows cardiac enlargement with Fallot configuration and poor pulmonary circulation at the periphery.

The electrocardiogram showed digitalis effect and Wolff-Parkinson-White syndrome, and will be discussed later. Blood examination revealed: hemoglobin —21.0 g; hematocrit—72 per cent; sed rate—38 mm, and a negative test for C-reactive protein. A cardiac catheterization was attempted unsuccessfully, because, shortly after the introduction of the catheter into the right atrium, the patient developed an extremely fast supraventricular tachycardia, and the procedure was abandoned as the patient went into severe shock.

A few days later, with a clinical diagnosis of tetralogy of Fallot, the child was taken to surgery and a cardiotomy by means of a total bypass of the heart and lungs was performed. During the surgical procedure the diagnosis was confirmed and the lesions corrected. Immediately following the operation the patient did well. Blood pressure was stabilized at 90/60 and color was excellent. Four hours later, however, an exploratory thoracotomy was performed for excessive bleeding. No specific bleeding points were found. The second procedure was well tolerated and the patient returned from surgery again with a stable blood pressure and good color. Ten hours postoperatively, the patient's condition rapidly deteriorated and cardiac arrest occurred. Immediate cardiac massage was followed by recovery; the patient was lucid and showed no evidence of neurologic damage. Blood pressure was maintained with Levophed® drip. A second cardiac arrest occurred four hours later. Resuscitation was again successful. Eighteen hours postoperatively the patient died.

AUTOPSY DATA

The important findings were:

(1) Hypertrophy and dilatation of the heart (173 g), especially the right ventricle
(2) Large interventricular septal defect
(3) Moderate degree of overriding aorta
(4) Patent foramen ovale
(5) Endocardial sclerosis involving the interventricular septum
(6) Excision of infundibular area of the right ventricle
(7) Closure of interventricular septal defect with Ivalon sponge

FINAL DIAGNOSIS

(1) Tetralogy of Fallot
(2) Endocardial sclerosis involving the interventricular septum
(3) Surgical correction of infundibular pulmonic stenosis and interventricular septal defect (Fig. 2).

ELECTROCARDIOGRAPHIC FINDINGS

A series of four electrocardiograms was taken before surgery. They all presented the same findings (Fig. 3).

Analysis: Rate: 117/min; P-R interval: 0.07 sec; QRS duration: 0.11 sec; QTc: 0.355 sec.

SÂP: plus 20° forward; SÂQRS: plus 85° marked backward (the transitional pathway in the horizontal plane lying between V_5 and V_6); SÂT: minus 45° forward; ST changes suggestive of digitalis effect; delta waves seen in multiple leads.

Discussion

The inspection of the limb leads suggests the diagnosis of Wolff-Parkinson-White syndrome, type A. However, the precordial leads, showing a backward orientation of the ventricular activation, are compatible with Wolff-Parkinson-White syndrome, type B. Although the record does not fall into the category of either one of the two types, as described by Sodi-Pallares and associates, we feel it can be accepted as a variation of type B, since it shows

that the ventricular activation takes place from the anterior to the posterior part of the chest. The peculiar orientation backward and downward could be the consequence of the combination of Wolff-Parkinson-White syndrome and right ventricular hypertrophy or the result of marked clockwise rotation.

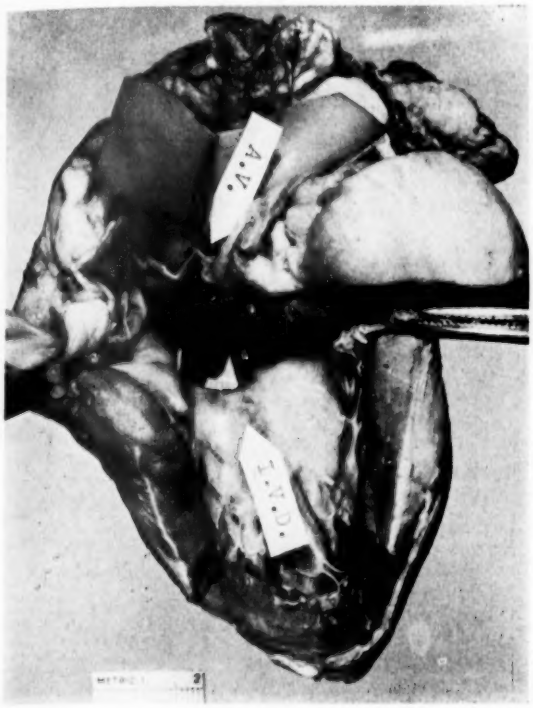

Fig. 2. Heart specimen. Note the large interventricular septal defect (I.V.D.) and the overriding aorta. A.V. = aortic valve.

As far as we know, there have been no reports in the literature describing the association of Wolff-Parkinson-White syndrome and tetralogy of Fallot. It could have been only a coincidence, since this electrocardiographic phenomenon may appear in any individual, even in the absence of evident cardiac disease. However, it seems interesting to point out that this child, as was stated in the autopsy data, presented marked endocardial sclerosis involving the interventricular septum (Fig. 4).

We do not know whether or not this change in the structure of the cardiac tissue at such a level could be responsible for the abnormal activation of the zone, in this way producing the shortness of the P-R interval and appearance of the delta wave. Nevertheless, there must be reasons to explain the hyperexcitability of this tissue, which becomes activated even by electronic diffusion of the auricular currents. Anatomic changes as such described above may be one of them.

Thus, we leave here a challenge for future investigations: May or may not endocardial sclerosis at the higher parts of the interventric-

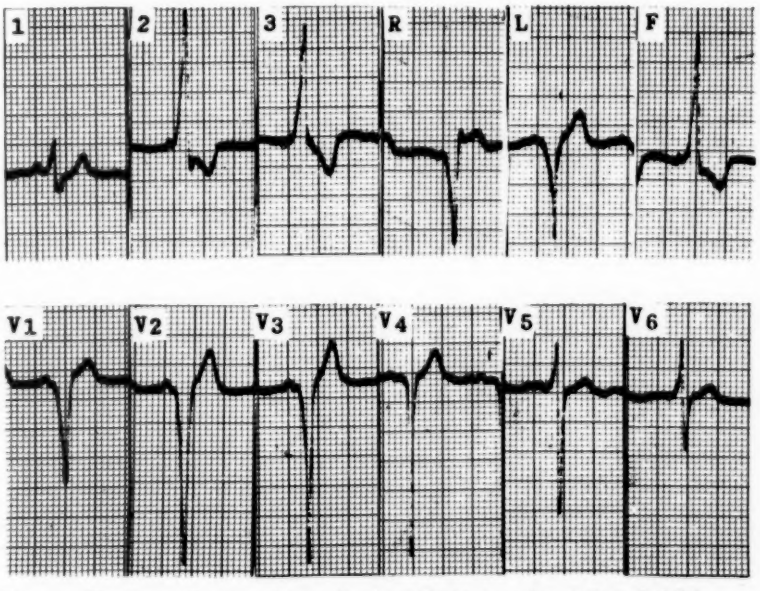

Fig. 3. Electrocardiogram shows the short P-R interval and broad QRS complexes; delta waves may be perfectly identified in lead 3. (See text.)

Fig. 4. High interventricular septum. (Verhoeff's Elastic-Van Gieson stain X240). Thickening of endocardium (sclerosis) with extension of fibrosis to the subendocardium layers. Dark wavy lines reveal elastica. The coarse fibrous bundles are collagen.

ular septum be responsible, in certain cases, for the development of the Wolff-Parkinson-White syndrome?

Summary

A case of tetralogy of Fallot proven at operation and autopsy presented the classic electrocardiographic findings of Wolff-Parkinson-White syndrome. An additional anatomic finding of interest was the presence of marked endocardial sclerosis involving the upper part of the interventricular septum. It is postulated that abnormal activation of this zone could have been responsible for the abnormal interventricular conduction.

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Tricuspid Stenosis and Insufficiency

Value of Jugular and Hepatic Pulse Tracings

HISTORY

THIS 33-year-old Negro female was admitted to the hospital because of fever, dyspnea, orthopnea, edema, malaise, and generalized weakness. Following a "cold," she became progressively more dyspneic and was coughing and spitting up blood.

The patient had acute rheumatic fever at the age of 12. She rested in bed for about four months. Frequent sore throats and transitory joint pains had been present since then. In 1953 she appeared at the clinic complaining of epigastric pain, night sweats, and shortness of breath, and was diagnosed as having rheumatic heart disease with mild decompensation. In November 1956, she reappeared at the clinic, complaining of palpitation, dyspnea, and frequent sore throats. She was treated with low salt diet, mercuhydrin and digitoxin. Her weight was 179 lb and progressively increased to 200 lb on her admission to the hospital.

PHYSICAL EXAMINATION

Physical examination revealed an orthopneic, dyspneic Negro female in acute distress. Temperature 101° F, pulse 100 to 120, with aperiodic irregularity, respirations 24, and BP 230/90. There was no icterus. The neck veins were distended and pulsating.

Examination of the chest showed crepitant

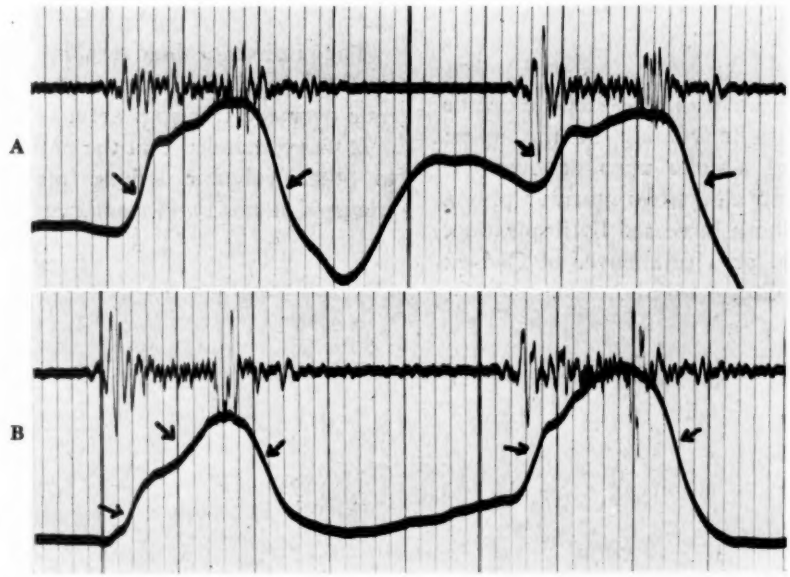

Fig. 1. (A) Jugular tracing simultaneous with phonocardiogram. (B) Hepatic tracing simultaneous with phonocardiogram. The arrows indicate the systolic plateaus, considered to be characteristic of tricuspid insufficiency.

rales in both pulmonary bases and expiratory wheezing. A systolic thrill was palpable over the base of the heart. The heart was markedly enlarged to the right and left on percussion. The PMI was in the left intercostal space at the anterior axillary line, 14 cm from the midsternal line. The apical rate was 120–130. A loud, rough systolic murmur was heard over the aortic area, transmitted to the neck. A loud systolic murmur was heard at the apex, transmitted to the axilla. No diastolic murmur was heard.

The liver was enlarged *14 cm below the right costal margin* and slightly tender. It was felt by some observers that the liver was pulsating. The hepato-jugular reflux was positive. There was 3 plus pitting ankle edema.

ELECTROCARDIOGRAM

The tracing revealed left ventricular hypertrophy, impure atrial fibrillation, and multifocal ventricular premature beats.

PHONOCARDIOGRAM

The tracing revealed an all-systolic murmur and a short diastolic rumble at the apex; a diamond-shaped systolic murmur over the aortic area, and an all-systolic murmur plus a diastolic rumble, both increased by inspiration, over the tricuspid area (maneuver of Chávez and Rivero Carvallo).

X-RAY EXAMINATION

The x-ray revealed a cor bovinum with enlargement of all chambers and evidence of pulmonary congestion.

DIAGNOSIS

The physical and graphic data led to the diagnosis of: rheumatic heart disease; mitral insufficiency and stenosis; aortic stenosis. A problem which was not solved was that of a possible tricuspid involvement.

Jugular and hepatic pulse tracings were recorded (Fig. 1). Both revealed a *systolic plateau with a slow rise and a slow drop.*

As known, both tracings present a clear drop during ventricular systole (systolic collapse) in persons with a normal tricuspid valve. Tricuspid insufficiency causes the appearance of a systolic plateau, i.e., a rectangular rise of the tracing. If it is "functional," both the rise and the drop are rapid. If on the contrary, it is "organic" and is associated with stenosis, the rise and fall of the "plateau" are slow.

The findings of these tracings were confirmed by the inspiratory increase of the systolic murmur over the tricuspid area.

It was concluded that the patient, in addition to other valvular lesions, also had organic tricuspid stenosis and insufficiency.

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Readers are invited to submit reports of interesting cases and illustrative tracings for this department. These should not exceed 1,000 words in length. Although not necessarily original, all material submitted should have teaching value.

Progress Notes in Cardiology

Edited by EMANUEL GOLDBERGER, M.D., F.A.C.C.

New York, New York

Investigators and research workers are invited to submit, with a view to publication in an early issue, résumés of work in progress or recently completed.

Inhalation Radiocardiography

A RECENT and interesting development in cardiology has been the use of radioactive tracer substances either by intravenous injection or by means of inhalation technics, to obtain information ordinarily obtained by cardiac catheterization. Numerous papers have appeared on this subject, including the following:

Donato and associates,[1] at the University of Pisa, have described the measurement of diastolic and residual blood volumes of the right ventricle by injection radiocardiography. They have given theoretical and clinical evidence of the value of this procedure in the diagnosis of mechanical abnormalities of the right heart.[2] The application of similar procedures to the left heart has been limited by the diluting effects introduced by passage of the radioactive tracer through the right heart and pulmonary circulation.

Determination of Diastolic and Stroke Volumes of Left Ventricle: This difficulty has been overcome by the use of an inhaled radioactive tracer, methyl radioiodide, by Drs. H. G. Thode, L. Donato, G. Debus, P. F. Nace, R. H. Tomlinson, and C. H. Jaimet[3] (Department of Medical Research, McMaster University, Hamilton, Ontario). They developed a method for measurement of the diastolic and stroke volumes of the left ventricle. With suitable instrumentation, aortic insufficiency, mitral stenosis, and mitral stenosis with regurgitation may be differentiated, and a quantitative estimate given of the severity of the lesion. Evidence has been obtained suggesting that a similar procedure may permit measurement of the coronary circulation.[4–6]

The methyl radioiodide was prepared by an exchange reaction of natural methyl iodide with sodium radioiodide. In a single inspiration, the patient inhaled approximately 1 mg of material, with 15 μc of activity. The passage of the activity through the left heart was observed by a 2 inch crystal scintillation counter centered at the left sternal margin of the 4th intercostal space. Through a pulse height analyzer and rate meter, the transit of activity was recorded on an Esterline-Angus pen recorder.

From a semilogarithmic plot of this recording, the cardiac output was calculated as percentage of diastolic ventricular volume. With the cardiac output measured by injection radiocardiography, the diastolic volume may be expressed in absolute units. For normal males, the values obtained were: diastolic volume—700 ml, stroke volume—17.5 per cent (123 ml); residual volume 82.4 per cent (577 ml). For normal females, the corresponding values were 630 ml, 20.5 per cent (126 ml), and 79.5 per cent (504 ml).

The descending limb of the curve reached a minimal level approximately 50 per cent of peak value. This final steady level has been shown to be due to activity trapped in the myocardium. Using radioactive Krypton^{85}, in place of the methyl radioiodide tracer, all the information obtained from the iodocardiogram was gained with the addition of a second exponential function considered to represent the coronary circulation. It has been found that this value, expressed as percentage of cardiac output, is lower in trained athletes than in normal subjects and much higher in known coronary disease pa-

tients. At present, this is a comparative measure, but investigations in progress promise to provide accurate quantitative measurement.

For the diagnosis of valvular and aortic abnormalities, it has been found important to record simultaneously the rate of passage of tracer into the lungs and the heart rate. This is accomplished by use of several counting circuits and detectors, connected to a multichannel recorder of low response time.

The procedure employed is entirely safe for the patient. It requires only a few minutes and can be repeated at any frequency desired. The equipment needed is relatively inexpensive and can be used for other isotope studies of thyroid, liver, kidney, lung, and peripheral circulation. In providing direct measurement in absolute units of the actual passage of blood through the chambers and valves of the heart, it is considered a valuable adjunct to established cardiologic procedures.

Detection of Intracardiac Shunts: Krypton^{85} has also been used by Drs. Richard J. Sanders and Andrew G. Morrow (National Heart Institute, Bethesda, Md.). Their use of the inert radioactive gas, Krypton^{85}, for the detection of left-to-right shunts is based upon the principle of the N_2O test (*Circulation* 17: 284, 1958) used for the same purpose. Immediately following the inhalation of Kr^{85}, its concentration in arterial blood rises rapidly. The tissues, which are devoid of the gas, remove most of it by absorption, so that almost none of it appears in venous blood, until the tissues become saturated.

Studies performed by Drs. Sanders and Morrow in experimental animals revealed that after 10 to 15 seconds of inhalation, the Kr^{85} content of normal venous blood was always less than 10 per cent of the arterial content. In the presence of a left-to-right shunt, however, arterial blood, containing Kr^{85} could mix with venous blood, so that samples obtained at or beyond the entrance of such a shunt had a Kr^{85} content well in excess of 10 per cent of the arterial content. The amount of radioactivity appearing in the venous circulation was directly proportional to the magnitude of the shunt.

The test has been performed during the course of right heart catheterization in more than 75 patients with various types of congenital and acquired heart disease. The catheter is positioned in the pulmonary artery or a right heart chamber, and a needle inserted into a systemic artery. The patient then inhales a mixture of Kr^{85} and air for 30 seconds, while integrated blood samples are simultaneously drawn from the catheter and the needle. The blood samples can each be analyzed for their radioactivity in one minute. The results of all tests are expressed as the ratio of the pulmonary arterial or right heart sample to the systemic arterial sample.

The pulmonary arterial test actually serves as a screening test, because if it is negative, the possibility of a left-to-right shunt at any level in the heart can be excluded, and additional tests need not be done. If the pulmonary arterial test is positive, a shunt is present and may be localized by repeating the test in the right ventricle and right atrium.

The preliminary results with the Kr^{85} test have indicated that it will detect the small shunts which are frequently missed with the method of measuring oxygen differences. The diagnostic criteria, as well as a method for the quantification of the magnitude of a shunt, are now being formulated. A preliminary report has already appeared.[7] The amount of irradiation received by the patient is inconsequential.

Krypton^{85} is better than ethyl iodide gas tagged with I^{131} which has also been used for this purpose, because I^{131} has a half-life of only eight days and therefore has to be obtained at frequent intervals. However, Kr^{85} has a half-life of about ten years.

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Cardiac Resuscitation

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New York, New York

Hypoxia: Its Environmental and Pathologic Etiology

THREE terms in common use, to describe a reduction of oxygen in the tissues, are asphyxia, anoxia, and hypoxia. Asphyxia means without pulse, anoxia, without oxygen, hypoxia, reduced oxygen. Since the term asphyxia is not descriptive, and anoxia is not accurate (there is always some oxygen present even in venous blood), hypoxia is coming into general use. Pending general adoption, however, we may be pardoned for using the three terms interchangeably.

DEFINITION OF ASPHYXIAL DEATH

References to asphyxial or hypoxic deaths occur frequently in the literature. The question immediately arises, how can we classify the causes of such deaths? Does not everyone die from cessation of the respiration and asphyxia? How can one pin-point a death as asphyxial? The answer depends upon two words: "because" and "in." If a victim is about to die "because" of asphyxia, the relief of such asphyxia will save his life. He will recover promptly and be as well as he was before the accident. This then could be classified as an impending asphyxial death. On the other hand, if one is dying "in" asphyxia, as from a malignancy causing respiratory obstruction, no amount of resuscitation will have any effect upon the terminal issue, except to postpone it. Such asphyxia is not an asphyxial death; asphyxia in this case is but a symptom. Asphyxial deaths are therefore demonstrable and definite entities. More than 50,000 of these deaths occur each year in the United States. As a world problem, it is conservatively estimated that at least 1,000,000 occur each year, one-half of these involving newborn babies.

PREVALENCE AND ETIOLOGY OF ANOXIA

The purpose of this article is to give the reader in as few words as possible, a bird's eye view of the total problem of asphyxia. Figure 1 suggests this. A moment devoted to a close inspection of this illustration will prove rewarding. The four forms or roots of anoxia should be committed to memory. Taken together, these add up to the total problem of asphyxia. This in turn may be separated into civilian and national defense problems, with further subdivisions into infant and adult, United States Public Health Service, Veterans, Army, Navy, and Air Force services.

The many environmental conditions in which the four forms of asphyxia may be expected to appear are as foliage on this tree. If one fails to appreciate the asphyxial pathology (hypoxic form) to be anticipated in these apparently disconnected accidents and does not group them automatically under the root from which they spring, it becomes difficult to apply the correct treatment. Each form, anoxic (obstructive), anemic (hemoglobin loss), stagnant (circulatory failure), and histotoxic (cell poisoning), will be found to include a whole family of acci-

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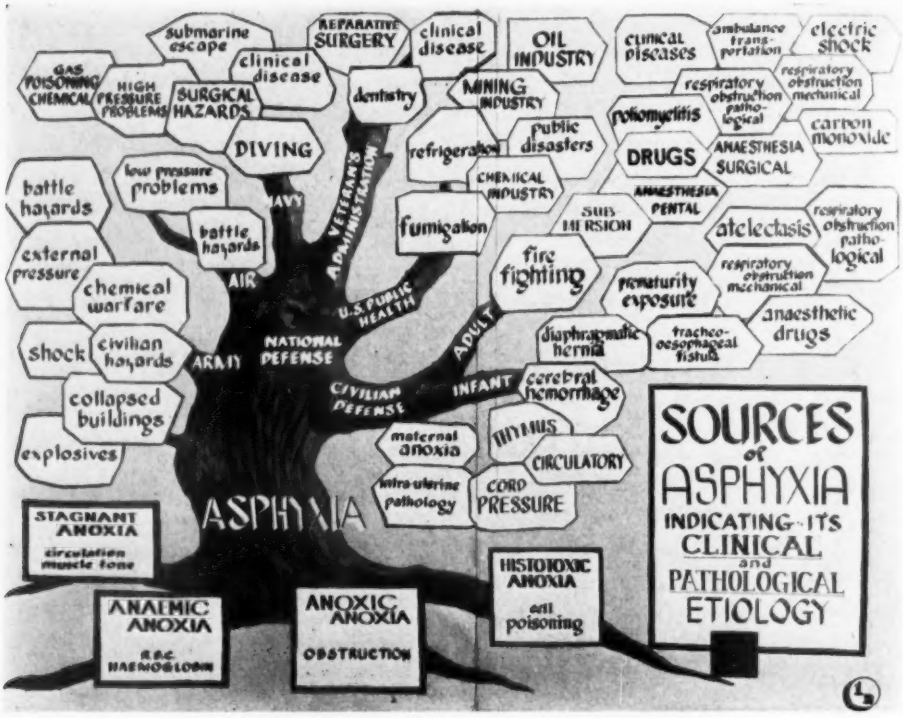

Fig. 1. Hypoxia cuts across the entire field of medicine.

dents which have no other common denominator or relationship. These include drowning, suffocation, asphyxia of the new born, mechanical respiratory obstruction, high altitude flying—all anoxic anoxia; or spinal anesthesia, drug poisoning, circulatory failure, oversedation, muscle relaxants—all stagnant anoxia. Furthermore, these root causes of hypoxia seldom occur separately. They are usually multiple, as is the case in an oversedated patient (stagnant hypoxia), suffering from hemorrhage (anemic anoxia) and from respiratory obstruction (anoxic anoxia).

Observing the total field one can understand why hypoxia cuts across the entire field of the practice of medicine. It is not only as prevalent as hemorrhage but hemorrhage produces its effects as anemic anoxia. A problem as universal as hypoxia cannot be left in the hands of a single specialty, such as anesthesiology, for disposition and control. Such an abandonment by the medical profession as a whole, may result in needless deaths. The magnitude of acute respirocardiac failure is such that it deserves sponsorship at the highest medical level in a spirit actuated by a desire for dissemination of knowledge and know-how. The American College of Cardiology suggests such a level and such detached altruism.

Environmental Factors in Asphyxia

Finally, the total field represented in Figure 1 is naturally divided into intramural and extramural accidents, those which occur inside and those which occur outside the hospital.

Intramural Asphyxial Accidents: As physicians we are more or less familiar with the intramural accidents to be met in the operating room, the recovery ward, and the accident ward. This familiarity has led us to become satisfied to leave these emergencies to others, to almost anyone, including the first aid squads, with resultant failure to save lives because of delay, lack of skill or more commonly because no organized service is immediately available. The immediate and spontaneous questions, "how" and "why," are quite academic and useless unless they have the effect of alerting an awakened "asphyxia con-

sciousness," a sensitivity to the phenomena which precede the fatal issue.

The rate, rhythm and the volume of the pulse are much less important than the rate, rhythm and amplitude of the respiration and the change of color of the mucous membranes accompanying respiratory failure. Improvement of the respiration may well improve the circulation; stimulation of the circulation cannot be expected to relieve an embarrassed respiration. Pink patients do not die. Blue patients may present a full bounding pulse masking a progressive hypoxia which invites cardiac standstill. The pale patient of hemorrhage may conceal an urgent anemic or stagnant hypoxia. Many years ago a polio patient in a respirator was allowed to gurgle mucous and gastric contents back and forth in his pharynx and trachea; today a meticulous toilet of the airway is regarded as mandatory. The well known death rattle of terminal disease is of course nothing more or less than the effect of progressive hypoxia expressing itself as disappearance of the swallowing reflex and relaxation of the soft parts of the airway. In the absence of an obvious cause of death which is irreversible, as cancer or an overwhelming septicemia, such a patient is entitled to suction of the airway and oxygen by nasal catheter. The major hazard of the intramural accident is that there is no warning. Protection of the patient turns upon the sensitivity to the signs of impending hypoxia. To be aware is to be alerted. To be alerted is to prevent asphyxial death.

Extramural Asphyxial Accidents: The extramural accidents, in the home, on the highway, in industry, on the beaches or in the sky, bring their own environmental warnings. We know that we must be prepared for hypoxia under these conditions. Again, the problem here is to appreciate the root form of hypoxia calling for treatment; in other words, what particular form of hypoxia does a given accident suggest. By immediately classifying such an accident, prompt and effective relief may follow. It is not enough to understand that electrocution, drowning, drug poisoning, carbon monoxide poisoning, preoperative and postoperative muscle relaxants, anaphylaxis, laryngeal spasm in dentistry, noxious gases, refrigeration, submarine escape, high altitude flying, etc., are basically hypoxic hazards rather than unique emergencies endangering life but it is important to classify each accident more specifically. Thus, one must realize that electrocution with one amp is stagnant hypoxia from ventricular fibrillation, drowning is anoxic anoxia; drug poisoning stagnant anoxia; carbon monoxide poisoning, anemic anoxia; muscle relaxants, stagnant hypoxia; anaphylaxis, anoxic anoxia; laryngeal spasm, anoxic anoxia; noxious gases, anemic and histotoxic with a complicating anoxic anoxia; refrigeration (CO_2), anoxic anoxia with a low O_2; submarine escape with aeroembolism, anoxic anoxia; and high altitude flying, anoxic anoxia (low O_2).

Importance of Etiologic Classification in Treatment of Anoxia

When such asphyxial accidents are identified according to their root forms, we may treat them as follows: *Anoxic anoxia*, by relieving respiratory obstruction and by improving the ambient atmosphere through added O_2; *anemic anoxia* by transfusion while providing O_2 inhalations; *stagnant anoxia* by circulatory support and increasing muscle tone through CO_2 stimulation in the oxygen administered (95% O_2, 5% CO_2); *histotoxic anoxia* by eliminating the cell poisoning such as alcohol, cyanides, sulfur gas, and supporting the patient meanwhile by O_2 administration.

To bleed the patient with anoxic anoxia, to sedate the one with anemic anoxia (for shock), to disregard positional treatment in stagnant anoxia (keeping the head elevated), or to sedate a patient with histotoxic hypoxia (alcohol), invites a fatal result. Eliminating the cause of the present hypoxia and the free use of oxygen will prevent asphyxial death.

The foregoing is by no means intended to suggest that every type of accident is hypoxic. It does emphasize, however, that a great many accidents formerly regarded as unrelated are actually bound closely together by the common bond of treatment, the administration of oxygen in a manner indicated by the degree of hypoxia faced at a given instant.

Use of Resuscitation Apparatus

The next issue of the Journal will suggest a unified approach to the total problem of hy-

poxia. It is believed that such an approach may be effected through a popularization of the behavior and the use of oxygen. Such knowledge should at least parallel what is known of the behavior and the use of common drugs such as morphine, digitalis, etc. Anyone who can read an electrocardiogram and treat a patient with cardiovascular disease can easily become familiar with the proper use of oxygen to save the life of such a patient. The internist's understanding of his patient is certainly better than that of an anesthetist called in an emergency.

The physician does not need lay mechanics in the form of a rescue squad to help him administer oxygen. If it is beneath his dignity to learn to use resuscitation apparatus to save the dying patient, such a patient would be better off in other hands. Any physician who can look into an ear can look into a larynx. Any physician who can pass a sound can pass an endotracheal tube in an unconscious relaxed patient. Popularization of the use of gases will serve to dispel the mystery associated with these simple procedures. Intensive courses of instruction presently provide this information. These courses should be multiplied over the country.

NOTE: Last April and June, (1958) a two-day intensive course in Acute Respirocardiac Failure was presented in New York City under the auspices of the National Resuscitation Society and The American College of Cardiology.

Applications are now being received for a repetition of this course to be presented in New York City, October 3–4, 1958.

Reprints of the material which is published monthly in this Section of the JOURNAL is mailed regularly to members of the National Resuscitation Society. Professional and technical workers in the field of gases for therapeutic purposes are eligible for membership.

For information write: Secretary, National Resuscitation Society, Inc., 2 East 63 Street, New York 21, N. Y.

Workmen's Compensation for the Cardiac

Problems and Plans of Study of the Committee

LOUIS H. SIGLER, M.D., F.A.C.C., *Chairman*

Brooklyn, New York

BEFORE discussing our problems and plans, it is advisable to present the following case which is fairly typical of the usual cases encountered in cardiac compensation claims. There are, of course, many variations and different angles in other cases of this nature.

TYPICAL CASE HISTORY

A male, fifty years old, who had general arteriosclerosis and hypertension, was standing on a step ladder five to six feet high, painting a ceiling. The ladder suddenly tipped while he reached out for the ceiling and fell down, hitting his anterior chest against a hope chest. He lost consciousness and fell to the floor. When admitted to the hospital, he showed evidence of posterior left ventricular wall infarction. He returned to light work about six months later, and to work as welder about eight months after the accident. He continued working without complaint for about four months, when he had an attack of left heart failure while lifting a heavy weight. Since then, he never returned to work because of weakness, shortness of breath, recurring precordial pain, visual disturbances and fainting sensations. There was progressive cardiac enlargement and congestive failure. Repeated electrocardiograms revealed the residual findings of the old posterior left ventricular wall infarction and progressive evolution of ventricular complexes indicative of recurring myocardial ischemia and of left ventricular hypertrophy and strain. About five years after the original accident, he developed paralysis of the right leg and motor aphasia, rapid increase in congestive failure, and died.

Autopsy revealed marked generalized arteriosclerosis. The heart weighed about 580 g. There was old organized thrombosis of the right coronary artery beginning about 0.5 cm from its origin and an organized old infarct of the posterior wall of the left ventricle in the form of dense fibrous connective tissue extending to a fourth of the adjacent interventricular septum. The remainder of the walls of the left and right ventricles were markedly thickened and dilated. The other coronary vessels showed atheromatous plaques but no occlusion. The liver was congested. There was an old organized infarct of the left kidney. The aorta showed considerable atheromatosis. The brain showed cloudy meninges, atheromatosis of the vertebral and middle cerebral arteries, softening of the left cerebral hemisphere and small cystic areas. The lungs showed arteriosclerosis of the pulmonary artery, pulmonary atelectasis and patchy bronchopneumonia.

QUESTIONS AND PROBLEMS RELATING TO THIS CASE

(1) Could the fall and the hitting of his chest produce his original coronary occlusion and posterior wall infarction if, as it was later claimed, there was some superficial thoracic wall injury? If so, what is the mechanism?

(2) Assuming that there was no thoracic wall injury produced by the fall, as the defendant claimed, is it possible that hitting his chest caused the myocardial infarction? If so, what is the mechanism?

(3) Is it possible that the coronary occlusion occurred spontaneously while standing on the ladder, and caused transient syncope, resulting in his falling off the ladder?

(4) Is it possible that the coronary occlusion was caused by the strain of standing on the ladder and stretching in the process of painting as well as in attempting to hold his balance? If so, what is the possible mechanism?

(5) Could the resulting heart damage be one of the causes of his subsequent cardiac hypertrophy and failure? If so, what is the mechanism?

(6) Did the later lifting of a heavy load on a job as a welder, under a different employer, in

any way contribute to his cardiovascular breakdown and subsequent complete disability of about four years as well as to his ultimate death? If so, how much did it contribute to his breakdown?

(7) If the subsequent course was merely due to progressive arteriosclerosis and hypertension, could we say that the original injury due to the fall was a contributory factor? If so, what percentage in monetary loss did the claimant sustain as a result of the original injury?

The studies to be pursued in our efforts to solve such problems, must, of necessity, include the following:

(1) Mechanism of injury resulting from natural hemodynamic changes in the course of time, that is the so-called "spontaneous attacks."

(2) Definitions of physical strain and trauma and of psychic strain, stress and emotion.

(3) Mechanisms of physical strain and trauma and of psychic strain and emotional stress in the initiation and/or acceleration of cardiac injuries.

(4) Clear-cut definition of disability due to such injury and its percentage in relation to injury caused by spontaneous and natural events.

(5) Length of time a person is to be considered disabled.

(6) Are future cardiac attacks occurring spontaneously to be related to an original insult?

(7) Can usual strain be a competent producing cause of injury?

(8) Criteria to be established as to causal relationship between trauma, strain and injury.

Investigations to Be Pursued

Medical Studies:

(1) Physics and dynamics of the circulation, to be fully reviewed and analyzed.

(2) Pathology and pathogenesis of coronary atherosclerosis, occlusion, myocardial infarction, ischemia or other injury.

(3) Statistical study of frequency of occurrence of "spontaneous attacks" and those following strain and trauma.

(4) Clinical evaluation of extent of injury induced by strain or trauma and that caused by the natural progression of disease.

(5) A study of the kinetic mechanism involved in traumatic injury of the heart.

(6) The relationship of trauma to atherogenesis.

(7) The immediate and long-term reactions of the myocardium to stresses of various kinds.

Legal Studies:

(1) Compensation laws in different states.

(2) Legal definition of trauma and strain.

(3) Statistical study of outcome of compensation claims in different states.

(4) Should cardiac disability occurring at work be covered by disability benefits other than Workmen's Compensation?

(5) Lump sum settlements.

(6) Should impartial panels of medical specialists be employed in compensation cases?

(7) Should pre-existing disease be considered in determining percentage to be paid for disability caused by strain or trauma?

Educational Program Suggested:

(1) Reports of our discussions in The American Journal of Cardiology.

(2) Dissemination of our findings among industries, attorneys and insurance companies.

(3) Ultimate publication of our studies in the form of a monograph, to be issued by the American College of Cardiology, covering the various cardiologic aspects of Workmen's Compensation.

The Query Corner

READERS are invited to submit queries on all aspects of cardiovascular diseases. Insofar as possible these will be answered in this column by competent authorities. The replies will not necessarily represent the opinions of the American College of Cardiology, the JOURNAL or any medical organization or group, unless stated. Anonymous communications and queries on postcards will not be answered. Every letter must contain the writer's name and address, but these will not be published.

Prediction of Acute Coronary Attack

Query: Can we predict an acute coronary occlusion? If so, can it be prevented?

Answer: Everyone is familiar with the story of the patient who received a clean bill of health from his physician and then proceeded to have a heart attack five minutes later on his way out of the office. Although this sequence of events is possible, it is highly improbable. Nevertheless, it does point out some of the uncertainty in predicting an attack.

There definitely are factors which are of some help in selecting those individuals who have an increased susceptibility to coronary disease. They include a strong family history of heart disease, hypercholesterolemia, obesity, diabetes, lack of physical exercise, stress, strain and nervous agitation with excessive pressure of work. However, considering such pertinent factors it still is difficult to be accurately predictive for any particular individual. It should be emphasized that the presence of mounting emotional tension bears more watching than it has enjoyed up to now in the epidemiology of heart disease.

The prediction of an imminent attack presents an entirely different problem. An individual who develops typical anginal pain for the first time or the one whose pre-existing angina pectoris becomes worse may well be on the road to an acute coronary occlusion and should be treated as such. Also, the susceptible individual as described above, if going through an unusually trying time with a tremendous emotional crisis, may be leading up to an attack. This is not too uncommon.

MORTON M. HALPERN, M.D.
Miami, Florida

Blood Cholesterol Reduction

Query: Is reduction of blood cholesterol and lipids by nicotinic acid, sitosterol, or unsaturated fatty acids of clinical value?

Answer: The absolute clinical value of the reduction of blood cholesterol and lipids remains to be established. However, there is enough evidence from various animal experiments, epidemiologic studies in man, and special clinical states to relate the serum concentration of cholesterol and lipids in a causal manner to the occurrence of atherosclerosis.

Nicotinic acid when tolerated is by far the most effective means in reducing the cholesterol and lipid fractions. In view of the difficulty of a quantitative measurement of the extent of atherosclerosis in man, the evaluation of the beneficial effects of reduction of cholesterol and/or lipids is practically impossible. The prevention by nicotinic acid of development of atherosclerosis in rabbits fed cholesterol is suggestive proof. In addition, the improvement of the ballistocardiogram in patients with coronary disease after reduction of the serum lipids is fairly good clinical proof.

It is generally accepted that patients with objective evidence of atherosclerosis should be placed on low-fat diets. One may overcome the objections and resistance to such a diet by using nicotinic acid even though the fats in the diet are not reduced; also by using sitosterol the same may be accomplished, but with much less effectiveness. Of the unsaturated fatty acids, corn oil is the most valuable, but must make up 70 per cent of the total fat intake.

MARTIN S. BELLE, M.D.
Miami, Florida

Book Reviews

Body Water in Man. The Acquisition and Maintenance of Body Fluids by Maurice B. Strauss. Little, Brown, Boston, 1957, pp. 286, $7.00.

In the preface to this urbane and erudite monograph, Dr. Strauss expresses his "main concern" as being a consideration of the mechanisms regulating the osmotic pressure and volume of the body fluids in man. The book is addressed primarily to the serious student and investigator of renal physiology, and the author realizes very well his hope that the material presented will afford a panoramic view of this field.

The book begins with a discussion of the phylogenetic development of mechanisms underlying osmotic and volume regulation of organisms as they evolved from sea water to fresh water and finally to land. There then follows, in the rest of the book, a discussion of the physiologic mechanisms regulating both the intake (thirst and appetite) of water and salt, and the renal excretion of these substances.

In addition to considering the commonly-accepted role of emotion and pain, various pharmacologic agents and increases in plasma osmotic pressure as stimuli to the secretion of the neurohypophyseal antidiuretic hormone (ADH), Dr. Strauss adduces the evidence, to which he himself has contributed, for the hypothesis that "the supra-optico-hypophyseal system is responsive to changes in the volume and distribution of the body fluids." The data on this subject are numerous, and at times conflicting, but the author summarizes them very persuasively. He also differentiates, fairly and distinctly, between fact and fancy.

Our knowledge of the physiologic disturbances of salt and water regulation in disease is less complete, and we are therefore confronted with important gaps in our understanding of the edema occurring in congestive heart failure, hepatic cirrhosis, and the nephrotic syndrome. But, as Dr. Strauss puts it in his concluding section, "the study of diseases has always been the flint from which have come sparks to light the beacon of physiologic understanding."

ABRAHAM G. WHITE, M.D.

Classics in Arterial Hypertension by Arthur Ruskin. Thomas, Springfield, Ill., 1956, pp. xxv plus 358, $9.50.

Of late, as readers of THE AMERICAN JOURNAL OF CARDIOLOGY are well aware, research on hypertension has been notably active and productive. The present time is therefore suitable for historical retrospect. Such retrospect, conducted carefully, makes intelligible the manner in which present concepts developed and is capable also of suggesting new routes of progress. Hence the history of his own branch of knowledge should not be disdained by a so-called practical investigator.

One tool for the formation of a retrospective view is the anthology, which presents a systematic selection of works that were composed in different eras. For the field of arterial hypertension such an anthology has been prepared by Dr. Arthur Ruskin, after the general pattern set by Major's *Classic Descriptions of Disease* and by the anthologies of Esmond Long on pathology and of Willius and Keys on cardiology.

The book opens with a rather incoherent 15-page introduction devoted mainly to pulse-lore, apoplexy, and venesection.

The text proper is divided into a section (pp. 3–133) titled *Methods* and another titled *Significance*. The section on methods contains excerpts from the writings of Hales, Poiseuille, Ludwig, Faivre, Marey, von Basch, Riva-Rocci, and Korotkov That on significance contains excerpts from the work of 17 men or groups of men, from Caelius Aurelianus to Goldblatt *et al.* Each author is introduced by a brief explanatory note, which serves as a sort of connective tissue that attaches the individual scientist to the general historical trend. At the end of the volume there is a list of more than a hundred references.

Dr. Ruskin's selections are highly instructive. Thus the reader will find: Stephen Hales' table which records the decline in the crural artery pressure of a mare subjected to progressive exsanguination (1733); his attempts to measure stroke volume and blood velocity; the excellent researches of Poiseuille on haemodynamics (1834); the remarkable studies on human circulatory function made by Faivre (1856); and two curious reports of Korotkov. The excerpts from Bright (1827), George Johnson (1852), Gull and Sutton (1872), F. A. Mahomed (1874), and Allbutt (1896) make an especially interesting series which explains the development of our knowledge concerning the relation between the kidneys and hypertension.

These examples are sufficient to demonstrate the value of the materials which are presented in Ruskin's anthology. This being the case, it is painful to report that the book is marred by bad proofreading, injudicious editing, and bad English. Here are a few sentences taken from various parts of the volume: Pulse-lore, unlike arterial pressure which became a routine clinical procedure fifty years ago, some 200 years after its first measurement (1711), goes back to antiquity. . . One justification of looking backward is that, though sometimes thought stultifying by the plodding, past eminences are inspiring to the brave. . . The same experiment was repeated in the presence of Monsieur *Cruveilhier*, who himself was willing to verify on the hemodynamometer of the carotid the deviations which announced my friend Doctor *Blandin*, etc. . . No sort of suitable remedies was omitted; nevertheless, in his weakened condition and about to expire I did not dare to open a vein. . . .

The inelegance of the translations is readily demonstrated by comparing Wepfer's report of the case of J. J. Reiter as given in the present anthology (pp. 146–148) with the translation given in Dr. Esmond Long's *Selected Readings in Pathology*, Springfield, 1929, pp. 75–77.

In summary, *Classics in Arterial Hypertension* can be recommended because of the valuable materials which it contains. The stylistic and other defects should be corrected in future editions.

SAUL JARCHO, M.D.

RECEIVED FOR REVIEW

All books received will be acknowledged in this column. Insofar as possible, as space permits, books of special interest will receive more extensive reviews.

Extracorporeal Circulation, compiled and edited by J. Garrott Allen, Thomas, Springfield, Ill., 1958, pp. 518, $7.50.

Peripheral Circulation in Health and Disease by Walter Redisch and Francisco F. Tangco, Grune and Stratton, New York, 1957, pp. 154, $7.75.

Die Neuzeitlichen Brustwand-und Extremitäten-Ableitungen in der Praxis by Helmut Kleipzig and Herbert Reindell, Georg Thieme Verlag, Stuttgart, 1958, pp. 192, D.M. 29.50 ($7.00).

Roentgenology of the Chest, edited by Coleman B. Rabin, Thomas, Springfield, Ill., 1958, pp. 484, $19.50.

High Arterial Pressure by F. H. Smirk, Thomas, Springfield, Ill., 1958, pp. 764, $15.00.

Heart Disease in Infancy and Childhood by John D. Keith, Richard D. Rowe, and Peter Vlad, Macmillan, New York, 1958, pp. 877, $22.50.

Laboratory Medicine—Hematology by John B. Miale, Mosby, St. Louis, 1958, pp. 735, $13.75.

Atlas und Kurzgefasstes Lehrbuch der Phonokardiographic und verwandter Untersuchungsmethoden by K. Hollack and D. Wolf, Georg Thieme Verlag, Stuttgart, 1958, pp. 179, D.M. 49.50 ($11.80).

Operable Herzleiden Einführung in Klinik, Diagnostik, und Operationsmöglichkeiten, by J. Jacobi and M. Loeweneck, Georg Thieme Verlag, Stuttgart, 1958, pp. 175, D.M. 49.50 ($11.80).

Portal Hypertension by Alan Henderson Hunt, E. & S. Livingstone, London, 1958 (Williams and Wilkins—American agent), pp. 230, $8.50.

Clinical Enzymology, edited by Gustav J. Martin, Little, Brown, Boston, 1958, pp. 241, $6.00.

Practical Cardiology by Albert Salisbury Hyman, McGraw-Hill, New York, 1958, pp. 307, $7.00.

Rehabilitation of the Cardiovascular Patient by Paul Dudley White, Howard A. Rusk, Philip R. Lee, and Bryan Williams, McGraw-Hill, New York, 1958, pp. 176, $7.00.

Bepaling van de Circulatie-Tijd Met een Foto-Electrische Methode (de Haemoreflector) (*Photoelectric Circulation Time Determination*) by S. Berrekloow, Drukkerij Poortpers N.V., Amsterdam, 1958, pp. 119.

Traite d'Anatomie Humaine, Volume 3, by George Paturet, Masson et Cie, Paris, 1958, pp. part I, 666, part II, 640, each part 12,000 fr.

Normale und Pathologische Entwicklung des Menschlichen Herzens by Klaus Goerttler, Georg Thieme Verlag, Stuttgart, 1958, pp. 123, D.M. 33 ($7.85).

Biophysical Principles of Electrocardiography by Robert H. Bayley, Hoeber, New York, 1958, pp. 237, $8.00.

Fundamentals in Cardiology by John B. Wild, Thomas, Springfield, Ill., 1958, pp. 83, $4.50.

College News

ELECTION OF OFFICERS FOR 1958–59

The following officers were elected at the Annual Meeting of the College in St. Louis on May 22, 1958.

PRESIDENT-ELECT
Osler A. Abbott, *Emory University, Ga.*

VICE-PRESIDENTS
Dwight E. Harken, *Boston*
Myron Prinzmetal, *Beverly Hills*
Ignacio Chávez, *Mexico City*

SECRETARY-TREASURER
Philip Reichert, *New York*

ASSISTANT SECRETARY
Henry I. Russek, *New York*

ASSISTANT TREASURER
Louis F. Bishop, *New York*

TRUSTEES (CLASS OF 1963)
Charles P. Bailey, *Philadelphia*
Samuel Bellet, *Philadelphia*
John S. LaDue, *New York*
Byron E. Pollock, *Denver*

George W. Calver, *Washington, D. C.*, was installed as the new President of the College.

HONORARY FELLOWS

At the Annual Convocation of the College, held on May 22, 1958, Honorary Fellowships were conferred on the following physicians for outstanding achievement in the field of cardiovascular disease:

Sir Russel Brock ..... *London*
Robert Bayley ..... *Oklahoma City*
Clarence Craford ..... *Stockholm*
Harry Goldblatt ..... *Cleveland*
Otto Loewi ..... *New York*

Honorary Fellows of the College who were elected previously are:

*Russel Burton Opitz, M.D. ..... *New York, N. Y.*
*W. E. Garrey, M.D. ..... *Lexington, Ky.*
*Rudolph Matas, M.D. ..... *New Orleans, La.*
Samuel A. Levine, M.D. ..... *Boston, Mass.*
Carl J. Wiggers, M.D. ..... *Cleveland, Ohio*
*Frank N. Wilson, M.D. ..... *Ann Arbor, Mich.*
Charles Laubry, M.D. ..... *Paris, France*
Cesare Frugoni, M.D. ..... *Rome, Italy*
Claude S. Beck, M.D. ..... *Cleveland, Ohio*
David Bruce Dill, Ph.D. ..... *Army Chemical Center, Md.*
William F. Hamilton, Ph.D. ..... *Augusta, Ga.*
John F. Fulton, M.D. ..... *New Haven, Conn.*
James Roscoe Miller, M.D. ..... *Evanston, Ill.*
Ignacio Chávez, M.D. ..... *Mexico City, Mexico*

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Ignacio Chávez, M.D. ..... *Mexico City, Mexico*
Simon Dack, M.D. ..... *New York, N. Y.*
Hannibal DeBellis, M.D. ..... *New York, N. Y.*
Elwyn Evans, M.D. ..... *Orlando, Fla.*
Seymour Fiske, M.D. ..... *New York, N. Y.*
Gabriel F. Greco, M.D. ..... *New York, N. Y.*
Dwight E. Harken, M.D. ..... *Boston, Mass.*
O. Henry Janton, M.D. ..... *Philadelphia, Pa.*
Samuel Korry, M.D. ..... *New York, N. Y.*
John S. LaDue, M.D. ..... *New York, N. Y.*
Aldo A. Luisada, M.D. ..... *Chicago, Ill.*
George R. Meneely, M.D. ..... *Nashville, Tenn.*
Max Miller, M.D. ..... *New York, N. Y.*
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Walter S. Priest, M.D. ..... *Chicago, Ill.*
Myron Prinzmetal, M.D. ..... *Beverly Hills, Calif.*
Philip Reichert, M.D. ..... *New York, N. Y.*
Henry I. Russek, M.D. ..... *New York, N. Y.*
I. Frank Tullis, M.D. ..... *Memphis, Tenn.*
Joseph B. Wolffe, M.D. ..... *Fairview Village, Pa.*

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Ashton Graybiel, M.D. ..... *Pensacola, Fla.*
Albert S. Hyman, M.D. ..... *New York, N. Y.*
Bruno Kisch, M.D. ..... *New York, N. Y.*
Attilio Robertiello, M.D. ..... *New York, N. Y.*
Epaminoda Secondari, M.D. ..... *New York, N. Y.*

PAST PRESIDENTS

*Franz M. Groedel, M.D. 1949–51
Bruno Kisch, M.D. 1951–53
Robert P. Glover, M.D. 1953–54
Ashton Graybiel, M.D. 1954–55
Walter S. Priest, M.D. 1955–56
Simon Dack, M.D. 1956–57
George R. Meneely, M.D. 1957–58

* Deceased.